Aripiprazole or Bupropion Augmentation Versus Switching to Bupropion in Treatment-Resistant Depression:

A Risk-Benefit Analysis

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Abstract

Objective: In treatment-resistant depression (TRD), augmentation with aripiprazole (A-ARI) or combination therapy by adding bupropion (C-BUP) has been reported as more effective than switching to bupropion (S-BUP), but C-BUP risks falls in older adults, and A-ARI risks weight gain and tardive dyskinesia (TD). The aim of this study was to clarify whether the enhanced effectiveness outweighs such risks.

Methods: In this risk-benefit decision analysis, lifetime quality-adjusted life-years (QALYs) following 1 year of A-ARI or C-BUP vs S-BUP treatment were simulated in a health-state transition model tracking depression remission, falls, weight gain, and TD, in age and baseline body mass index (BMI) subgroups, using data from the VAST-D and OPTIMUM trials and other literature. QALYs were converted to depression-free day-equivalents (DFDs), the QALYs gained from 1 day of remitted versus active depression.

Results: Simulated adults aged 18–64 years experienced a net benefit of C-BUP over S-BUP of 20.7 DFDs, equivalent to about 3 weeks of faster remission of depressive symptoms. In older adults, especially those aged 85+ years, this benefit over S-BUP was partially but not fully offset by a risk of falls. In adults aged 18–64 years, A-ARI was estimated to offer only 8.0 DFDs after subtracting the expected harms from TD, and this was further reduced to −22.8 DFDs once metabolic harms were considered, in those overweight at baseline. Overall, C-BUP was preferred over A-ARI in all subgroups except ages 85–89 years with BMI < 25, in whom A-ARI was preferred.

Conclusion: In our model, C-BUP better balanced efficacy and tolerability in TRD in adults under 85 years than did S-BUP or A-ARI. A-ARI was least-preferred in overweight adults. These results may inform shared decision-making and clinical guidelines.

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Treatment-resistant depression (TRD) is commonly defined as a depressive episode with insufficient response to 2 or more antidepressant therapies of appropriate dose and duration.[1] Thirty percent of prevalent cases of major depressive episodes on pharmacologic treatment meet criteria for TRD.[2] TRD patients have longer episodes, worse outcomes, and higher rates of suicide than do patients with uncomplicated depression.[3–6] Among other treatment options in TRD, common treatments include switching to the atypical antidepressant bupropion (S-BUP), combination therapy by adding bupropion (C-BUP), and augmentation with the second-generation antipsychotic aripiprazole (A-ARI).[7–9] It is unknown how best to prioritize among these treatment options to balance their risks and benefits.

Recently, S-BUP, C-BUP, and A-ARI were compared in 2 large randomized controlled trials in TRD: VA Augmentation and Switching Treatment for Depression (VAST-D)[10] and Optimizing Outcomes of Treatment-Resistant Depression in Older Adults (OPTIMUM),[11] demonstrating greater effectiveness in C-BUP and especially A-ARI over S-BUP but also an increased risk of significant side effects. These side effects included falls in older adults with C-BUP and weight gain and tardive dyskinesia (TD) with A-ARI. Falls in the elderly are a major contributor to reduced mobility and independence,[12] weight gain increases the risk of

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Clinical Points

- Aripiprazole has gained attention as an effective augmenting agent in treatment-resistant depression, but it is unclear whether it is worth its side effects.
- According to our model, bupropion augmentation may offer a better balance of risks and benefits on average than does aripiprazole augmentation.

diabetes and cardiovascular disease,[13,14] and TD is potentially disfiguring and typically permanent.[15,16]

It is unclear whether the greater benefits of A-ARI and C-BUP are worth their greater risks, either overall or for particular patient subgroups. The trial authors recommended that subsequent decision analyses integrate the risks and benefits of these treatments.[10] At the time of manuscript preparation, however, only 1 decision analysis had cited these trials, and that analysis focused on economic considerations, did not explicitly model side effects, and recommended further exploration of side effects for future research.[17] This is an important gap in research on TRD treatment because the differences in side effects between these treatments are a major driver of shared decision-making.

To address this gap, we performed a risk-benefit analysis comparing A-ARI and C-BUP to S-BUP in TRD. We assessed risk-benefit separately in different patient subgroups to better reflect the differential risks of these three treatments in different patient populations.

METHODS

Overview

We performed a type of risk-benefit analysis termed incremental net health benefit analysis[18] of C-BUP and A-ARI vs S-BUP among TRD patient subgroups defined by age and metabolic risk. Quality-adjusted life-years (QALYs) for each treatment and subgroup were calculated as the benefits from improved depression minus the harms of selected side effects. Side effects were prioritized in the model if they had differential incidence between treatments and had a propensity to cause long-term harm, which is where decision models have the greatest advantage over trial-and-error approaches.[19] Serious falls, clinically significant weight gain, and TD were prioritized for modeling on the basis of evidence that these side effects tend to result in long-term harms, whereas anxiety, insomnia, akathisia, somnolence, and other acute extrapyramidal symptoms were not included in the model because they are readily reversible upon treatment discontinuation.

We considered only health effects and not financial costs because no major payer or regulatory body advocates for restricting access to these treatments on the basis of small differences in generic prescription costs.

We conform to the 2022 Consolidated Health Economic Evaluation Reporting Standards guideline where applicable.[20] Analysis was conducted in R, version 4.4.0 (R Foundation for Statistical Computing). This analysis of public data was determined exempt from institutional review board review by the Mass General Brigham Institutional Review Board, #2024P001823. The analysis plan was not pre-registered. The text of the manuscript provides a summary of this project's methods; detailed methods including detailed parameter derivations and code to reproduce findings are described in an accompanying report.[21]

Model

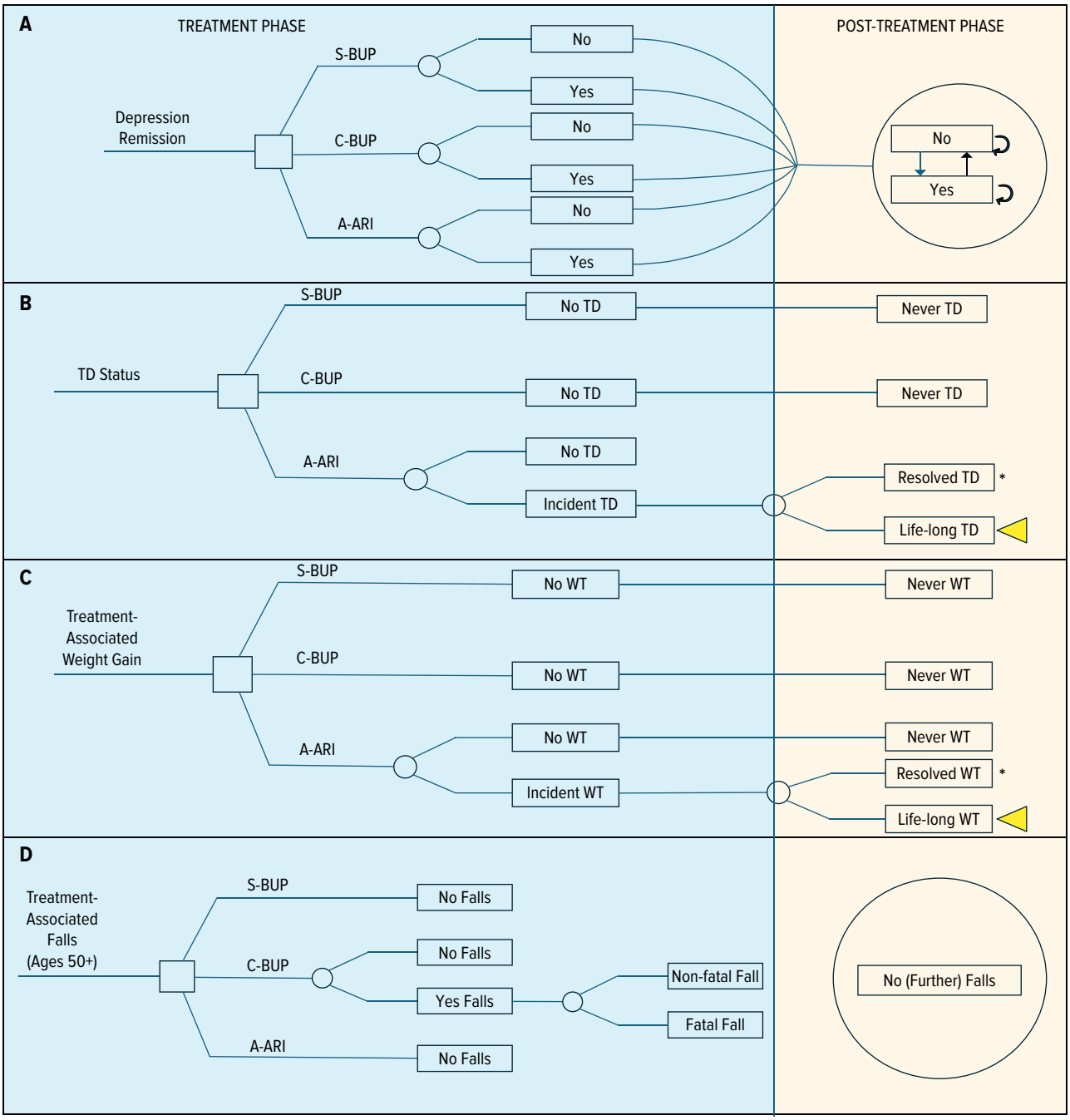
We used a health state transition model with 16 health states defined by the joint presence or absence of 4 health outcomes: depression, falls, weight gain, and TD, with death as the 17th state. Each adverse health outcome incurred an associated utility decrement derived from the literature and then summed across outcomes to yield the total utility of a health state. QALYs were converted to depression-free day equivalents (DFDs) for interpretability, where 1 DFD = 0.0012 QALYs, the value of living with remitted rather than active depression for 1 day. Simulated patients started with active depression and no side effects and transitioned between states of the model annually according to a transition probability matrix.

Time horizon. Simulations continued until patients' death (lifetime time horizon) in the base case to account for the long-lasting nature of some side effects of treatment. Death occurred according to age-adjusted and health-state–adjusted mortality rates.

Treatment duration. The simulation included a treatment phase and posttreatment phase. The treatment phase lasted 1 year, consistent with treatment guidelines for nonrecurrent depression[8] and approximately comparable to the continuation phase of VAST-D.[22] In the main analysis, the posttreatment phase lasted from the 1-year mark until the patient's death. During the posttreatment phase, patients receive a standard-of-care treatment and, unlike in the treatment phase, can experience cycles of relapsing and remitting depression that are independent of initial treatment choice. The logic and flow of health outcome transitions between phases are depicted in Figure 1.

State transitions. Transition probabilities for health outcomes differed by treatment strategy and patient subgroup, using data from VAST-D and OPTIMUM where possible and the broader literature where indicated, prioritizing systematic reviews. Excess falls were only modeled in adults aged 50 years or older on C-BUP. TD was only modeled in A-ARI. Relative net weight gain was only

Figure 1.
Model Diagram[a]



[a]In the main analysis, patients begin with active depression and without side effects and develop remitted depression, tardive dyskinesia (TD), weight gain (WT), and falls during treatment (blue panel) with probabilities that depend on patient subgroup and treatment strategy. After treatment (orange panel), weight gain and TD that arose on treatment have a chance of persisting indefinitely (orange triangles), while falls do not, and depression cycles between active and remitted states with fixed probability estimated from prior naturalistic follow-up studies. Note that the effects of resolved TD and resolved weight gain (asterisks) are handled as preprocessing steps (see Supplementary Material) and not separate states of the health transition model.
Abbreviations: A-ARI = augmentation with aripiprazole, C-BUP = combination therapy with bupropion, S-BUP = switch to bupropion.

modeled in A-ARI and only tracked in subgroups with elevated baseline body mass index (BMI > 25) in the base case, since it is in this population where additional weight gain is most clinically relevant[23] (this latter constraint was relaxed in a sensitivity analysis). Transition probabilities between health states were modeled as the product of the transition probabilities between health outcomes, normalized so that matrix

Table 1.
Description of Included Studies

Study	Population	Intervention	Duration
VAST-D acute phase[10]	1,522 veterans (85% male) with MDD, mean age = 54 years, who failed 1+ antidepressants (median of 2) Mean baseline QIDS-C_{16}: 16.7 Definition of failed trial: eg, QIDS-C_{16} ≥ 11 after 8 weeks, including 3 at optimized dose Index treatment before study start: SSRI (78.5%), SNRI (18.4%), or mirtazapine (3.1%)	Randomized to S-BUP vs C-BUP vs A-ARI	12 wk
VAST-D continuation phase[22]	725 participants from VAST-D acute phase who responded during the acute phase	Continued on acute phase agents	36 wk cumulative
OPTIMUM[11]	617 older adults at academic centers (33% male) with MDD, mean age = 69, who failed 2+ antidepressants Mean depression PHQ-9: 15.8 Definition of failed trial: PHQ-9 ≥ 6 after 12 wk between 2 antidepressant trials, revised 18 months after start to be PHQ-9 ≥ 10 Index treatment before study start: SSRI (50.2%), SNRI (39.6%), mirtazapine (5.2%), bupropion (2.7%), serotonin modulators (2.1%), tricyclic (0.2%), MAO-I (0.2%)	Randomized to S-BUP vs C-BUP vs A-ARI (Phase 1)	10 wk (Phase 1)

Abbreviations: A-ARI = augmentation with aripiprazole, C-BUP = combination therapy with bupropion, MAO-I = monoamine oxidase inhibitor, MDD = major depressive disorder, PHQ-9 = Patient Health Questionnaire-9, QIDS-C_{16} = Clinician-Rated Quick Inventory of Depression Symptomatology, S-BUP = switch to bupropion, SNRI = serotonin-norepinephrine reuptake inhibitor, SSRI = selective serotonin reuptake inhibitor.

rows summed to 1. Simulations were implemented in the *hesim* R package (v. 0.5.5).[24]

Discount rate. In health economic analyses, it is conventional to down-weight the importance of health effects and economic consequences of treatments that occur years in the future; the speed of this down-weighting is referred to as the temporal discount rate. In the base case, the temporal discount rate was set at 1.5%, as recommended by the National Institute for Health and Care Excellence when treatments entail long-term health effects, as applies to TD and weight gain.[25] Financial considerations favoring higher discount rates in cost-effectiveness studies do not apply to risk-benefit analyses like ours that do not model financial costs. At our temporal discount rate, the experience of living with TD or consequences of weight gain for 1 year 10 years in the future is assigned $(1-r)^{10} = 86.0\%$ as much importance as living with these consequences this year.

Included studies. VAST-D and OPTIMUM have been previously described and are briefly summarized in Table 1. Of note, while all participants in OPTIMUM and the majority in VAST-D had 2 or more failed antidepressant trials, some participants in VAST-D had had only 1 prior failed antidepressant trial.

Subgroups

We applied the model separately to 8 patient subgroups defined by age and baseline BMI, chosen for their relevance for the modeled side effects. Age strata included adults aged 18–64 years, 65–84 years, and 85–89 years. These age bin cut points were chosen by first visualizing QALYs along the entire age distribution and then collapsing ages with similar QALY profiles. BMI was defined as nonelevated (18 < BMI < 25) or elevated (BMI ≥ 25).

Inputs

Chosen inputs, their confidence intervals, and fitted distributions are shown in Table 2. In brief, depression remission rates on treatment, the relative risk of falls on C-BUP, and the net increased incidence of clinically significant weight gain (≥7% of baseline) on A-ARI were derived from OPTIMUM and VAST-D. The annual incidence of lifelong TD on second-generation antipsychotics such as A-ARI was derived from a systematic review and meta-analysis[26] then adjusted for the lower dosages used in depression,[27] the higher risk in older adults,[28] and spontaneous remission rates.[29] The base rate of mortality by age was obtained from lifetables released by the Social Security Administration. The base rate of serious falls by age was obtained from the CDC Web-based Injury Statistics Query and Reporting System (WISQARS),[30] which was then increased in C-BUP according to the relative risk of falls under C-BUP reported in OPTIMUM. In the main model, net weight gain with A-ARI is defined as a between-arms comparison, which implicitly encodes any weight loss with S-BUP and C-BUP (a raw change-from-baseline value is also included as a sensitivity analysis). All utility values were derived from systematic reviews, except for TD, for which we performed our own synthesis of available direct and indirect utility assessments.[31–33]

Input Validation

To gauge the external validity of model inputs, we compared our inputs with independent estimates, with a focus on providing reference points, rather than formal hypothesis testing, as in prior decision analyses.[39] The pairwise relative risks of depression remission by treatment strategy of the model were compared with

Table 2.
Model Parameters

Parameter	Value (95% CI) [selected univariate sensitivity analyses]	Distribution	References
Time horizon	Lifetime [20 y]		
Temporal discount rate	1.5% [3%, 0%]		
Depression remission rate on S-BUP	0.215 (0.186 to 0.246)	Beta	10,11
Depression remission rate on C-BUP	0.273 (0.241 to 0.306)	Beta	10,11
Depression remission rate on A-ARI	0.289 (0.256 to 0.324)	Beta	10,11
Post-treatment proportion of years remitted	0.415 (0.413 to 0.417)	Beta	34
Relative risk of falls on C-BUP	1.56 (1.24 to 1.97)	Normal	11
Annual incidence of TD on A-ARI	0.011 (0.009 to 0.013)	Beta	26,27,29
Incidence of weight gain on A-ARI	0.351 (0.294 to 0.411)	Beta	22
Mortality hazard ratio per BMI >25	+0.042 (0.040 to 0.044)	Beta	23
Utility active depression	−0.628 (−0.758 to −0.498)	Beta	35
Utility remitted depression	−0.197 (−0.255 to −0.139)	Beta	36
Utility clinically significant fall	−0.135 (−0.181 to −0.090)	Beta	37
Utility per BMI >25	−0.004 (−0.006 to −0.001)	Beta	38
Utility TD	−0.061 (−0.094 to −0.028)	Beta	31–33

Abbreviations: A-ARI = augmentation with aripiprazole, BMI = body mass index, C-BUP = combination therapy with bupropion, S-BUP = switch to bupropion, TD = tardive dyskinesia.

estimates from a network meta-analysis[40] and from a smaller randomized controlled trial of A-ARI vs C-BUP.[41] The observed number of incident cases of TD in VAST-D continuation phase was compared against our model's meta-analysis-derived TD rate. Raw weight gain rates from VAST-D continuation phase were compared against an earlier 1-year study of A-ARI in depression[42] as well as on a per-week basis from a meta-analysis of short-term study of aripiprazole.[43] We compared our OPTIMUM-based estimate of the fall risk associated with C-BUP in older adults with one from a study that performed a before-after comparison of fall rates in older adults starting C-BUP.[44] In some cases, model attributes were transformed to be more conceptually similar to the external comparison, and so the model attributes used in validations were not identical to model parameters.

Probabilistic Sensitivity Analyses

To account for parameter uncertainty, during successive runs of the model, parameters were simultaneously drawn from their 95% confidence intervals according to their fitted distributions as reported in Table 1.

Univariate Sensitivity Analyses

We completed 7 sets of univariate sensitivity analyses to test the impact of our assumptions regarding temporal discount rate, time horizon, falls, TD, and weight gain:

1. Temporal discount rate set to 3% or 0% instead of 1.5%.
2. Time horizon reduced to 20 years from lifetime (shorter than this was judged to not appropriately capture the consequences of lifelong TD or premature death).
3. Duration of disability after serious falls increased to 2 years to account for prolonged physical deconditioning and fear of falling after serious falls in older adults.[45]
4. TD incidence rates derived from aripiprazole studies specifically, a point estimate 35% lower than second-generation antipsychotics class rates.[26]
5. Weight gain modeled as fully reversible after 3 years.
6. Weight gain with A-ARI calculated as change from baseline without comparison to the weight-loss agent bupropion.
7. Weight gain considered also clinically relevant in the estimated 29% of patients of nonelevated weight who would naturalistically later develop elevated BMI within 10 years.[46]

RESULTS

Input Validation

For external validation of model inputs, we compared depression remission rates and the incidence of TD, weight gain, and falls on the studied treatments with independent estimates of these rates. For all key rates, the values implied by our chosen model were directionally aligned with the independent estimate, and of qualitatively similar magnitude (Table 3).

In particular, the risk of weight gain with long-term aripiprazole treatment in depression in the VAST-D continuation phase, 30.6%, was similar to the 36.6% reported in a large, earlier study.[42] Moreover, the average estimated weight gain per week of A-ARI

Table 3.
Validation of Key Attributes of Health States of Model

Health state: key attribute	Source of modeled estimate	Source of independent estimate	Values implied by model (95% CI)	Value from independent estimate (95% CI)
Depression: Increased relative risk of remission in C-BUP vs antidepressant monotherapy	VAST-D and OPTIMUM	Network meta-analysis[40]	1.27 (1.05–1.53)	1.32 (0.86 to 2.02)
Depression: Increased relative risk of remission in A-ARI vs antidepressant monotherapy	VAST-D and OPTIMUM	Network meta-analysis[40]	1.35 (1.12 to 1.61)	1.75 (1.47 to 2.09)
Depression: Numerically increased relative risk of remission in A-ARI vs C-BUP	VAST-D and OPTIMUM	Smaller RCT in TRD[41]	1.06 (0.90 to 1.25)	1.63 (1.02 to 2.58)
Weight: % of patients on A-ARI experiencing clinically significant weight gain	VAST-D continuation phase at 36 wk	Large RCT in TRD at 52 weeks[42]	30.6% (25.2% to 36.5%)	36.6% (31.3% to 42.1%)
Weight: Average weight gain from aripiprazole in kg/week	VAST-D continuation phase at 36 wk	Meta-analysis of short-term RCTs[43]	0.05 (0.04 to 0.06)	0.12 (0.03 to 0.21)
TD: Number of incident cases of TD expected in a trial with sample size, duration, and age distribution of VAST-D continuation phase	Derived from systematic review and meta-analysis	Observed number of TD cases in VAST-D continuation phase[22]	5.6 (1 to 11)	2
Falls: Risk of falls in older adults on C-BUP vs antidepressant monotherapy	OPTIMUM	Before-after comparison in 18 older adults[44]	RR 1.56 (1.24 to 1.97)	OR 3.51 (1.35 to 9.15)

Abbreviations: A-ARI = augmentation with aripiprazole, BMI = body mass index, C-BUP = combination therapy with bupropion, OR = odds ratio, RCT = randomized controlled trial, RR = risk ratio, S-BUP = switch to bupropion, TD = tardive dyskinesia, TRD = treatment-resistant depression.

participants in VAST-D continuation phase was 0.05 (0.04–0.06) kg per week, which was similar to and not greater than the meta-analysis-implied weight gain per week of 0.12 (0.03–0.21) kg/week.

Base Case

Preferred treatment strategies by subgroup. The expected incremental net health benefit (INHB) of C-BUP and A-ARI, relative to S-BUP, is reported in Table 4 for each patient subgroup, along with the breakdown in terms of DFDs gained or lost due to efficacy and each modeled side effect. 95% confidence intervals in the table were derived using simultaneous sampling of parameters from their distributions as a probabilistic sensitivity analysis. For almost all subgroups, C-BUP achieved the best balance of efficacy and tolerability. The exception was in adults aged 85–89 years of nonelevated weight for whom A-ARI was the preferred treatment, offering 3.0 more DFDs than C-BUP and 10.9 more DFDs than S-BUP. In the base case, S-BUP was not the preferred treatment for any subgroup.

C-BUP efficacy and tolerability. For all subgroups, C-BUP was preferred over S-BUP. For adults under 65 years, the magnitude of the INHB of C-BUP over S-BUP was equivalent to remission of depression 3 weeks earlier on average. Among older adults, these gains were partially offset by an increased risk of falls, which was pronounced in the aged 85–89 years cohort. Most of the harm from falls came from nonfatal falls, but fatal falls had some impact. In the base case, the harms from falls were not enough to outweigh the benefits of C-BUP over S-BUP at any age.

A-ARI efficacy and tolerability. A-ARI was preferred over S-BUP among patients with nonelevated weight, whereas S-BUP was preferred in patients who were overweight at baseline. In adults under 65 years, A-ARI offered 27.3 additional gross DFDs of depression efficacy compared to S-BUP, but this was partially offset by side effects in nonelevated weight individuals and more than offset by side effects in overweight individuals. The harms from TD offset 56%–81% of the depression benefit of A-ARI over S-BUP and had a complex relationship with age, with younger patients being affected by TD for more years but older patients having a higher relative risk of incident TD. Among patients who were overweight at baseline, weight-related side effects of A-ARI relative to S-BUP were substantial and were 95%–131% as large as the depression benefit of A-ARI over S-BUP. The impacts of relative weight gain from A-ARI on quality of life were highest in adults under 65 years who were overweight at baseline. The relative contribution of weight gain on DFDs from A-ARI in adults of elevated weight was larger via the mortality effect than via the quality-of-life effect.

Probabilistic Sensitivity Analysis

The results of the probabilistic sensitivity analysis for preferred treatment strategies by subgroup are reported in Table 4. For 4 of the 6 subgroups, the preferred strategy in the base case was preferred in more than 80% of probabilistic sensitivity analysis runs. The most uncertainty in treatment selection was for the oldest subgroup. In adults aged 85–89 years of nonelevated weight, A-ARI, C-BUP, and S-BUP were favored in 58.8%,

Table 4.

Preferred Treatment and Breakdown of Risks and Benefits by Subgroup

	C-BUP DFDs				A-ARI DFDs					Preferred treatment in 1,000 PSA runs (%)		
Age bin	Net (95% CI)	DQ	FQ	FM	Net (95% CI)	DQ	WQ	WM	TQ	S-BUP	C-BUP	A-ARI
BMI not elevated												
18–64 y	20.7 (3.5 to 41.4)	21.2	0.4	0.1	8.0 (−15.1 to 32.4)	27.3	0	0	19.3	0.5	87.5	12
65–84 y	16.6 (0.0 to 37.0)	20.5	3.0	0.9	5.1 (−19.3 to 29.2)	26.5	0	0	21.4	1.8	83	15.2
85–89 y	7.9 (−9.4 to 29.2)	19.2	8.0	3.3	10.9 (−7.6 to 31.8)	24.6	0	0	13.7	5.2	36	58.8
BMI elevated												
18–64 y	20.7 (3.5 to 41.4)	21.2	0.4	0.1	−22.8 (−50.2 to 3.8)	27.1	14.4	16.3	19.2	0.6	99.4	0
65–84 y	16.6 (0.0 to 37.0)	20.5	3.0	0.9	−14.8 (−42.1 to 11.4)	26.5	5.6	14.3	21.4	2.5	96.8	0.7
85–89 y	7.9 (−9.4 to 29.2)	19.2	8.0	3.3	−1.3 (−21.1 to 20.6)	24.6	2.5	9.7	13.7	15.8	70	14.2

Abbreviations: A-ARI = augmentation with aripiprazole, BMI = body mass index, C-BUP = combination therapy with bupropion, DFD = depression-free day-equivalent (1 DFD = 0.0012 quality-adjusted life-years), DQ = DFDs gained due to improved quality of life from remitted depression, FM = DFDs lost due to increased mortality from falls, FQ = DFDs lost due to worsened quality of life from falls, PSA = probabilistic sensitivity analysis, S-BUP = switch to bupropion, TQ = DFDs lost due to worsened quality of life from tardive dyskinesia, WM = DFDs lost due to increased mortality from weight gain, WQ = DFDs lost due to worsened quality of life from weight gain.

36.0%, and 5.2% of runs, respectively. In adults aged 85–89 years of elevated BMI, C-BUP was preferred in 70.0% of runs, S-BUP in 15.8% of runs, and A-ARI in 14.2% of runs. A-ARI was favored in at least 12.0% of runs for all subgroups involving nonelevated weight.

Univariate Sensitivity Analyses

The preferred treatment for each subgroup was unchanged regardless of whether the temporal discount rate was set at 0%, 1.5%, or 3% (Supplementary Table 1). The preferred treatment for each subgroup was unchanged by shrinking the time horizon from lifetime to 20 years. Modeling disability from nonfatal falls as persisting for 2 years rather than 1 year did not change preferred treatments. Modeling weight changes as fully reversible after 3 years did not change the preferred treatment for any subgroup. Likewise, ignoring the weight loss impacts of bupropion did not change the preferred treatment for any subgroup. However, allowing for some harms of weight gain to accrue to people of nonelevated weight led to a slight edge in C-BUP over A-ARI in adults aged 85–89 years of nonelevated weight.

DISCUSSION

Among switching to bupropion (S-BUP), combination therapy with bupropion (C-BUP), and augmentation with aripiprazole (A-ARI), C-BUP offered the best overall balance of effectiveness and tolerability for TRD in the base case of our INHBs model for all but 1 patient subgroup. The exception was that for adults aged 85–89 years of nonelevated weight, A-ARI was preferred because of the risk of falls with C-BUP. Although S-BUP was not the most preferred treatment for any patient subgroup in the base case, it was superior to A-ARI in all subgroups with high baseline BMI.

These results were robust, at least in under age 85 years. In adults under 85 years, C-BUP was the preferred treatment in 8 of 8 univariate sensitivity analyses and >80% of all runs of probabilistic sensitivity analysis. Moreover, model parameters had external support as assessed in 7 tests for external validity.

The additional efficacy of A-ARI over C-BUP for depression was estimated to be the equivalent of about 1 week earlier remission of depressive symptoms. Against the backdrop of this slim efficacy differential, side effects were more influential as to which treatment was more favorable overall. The small risk of permanent TD on A-ARI amounted to an expected QALY loss equivalent to 2–3 weeks of additional depressive symptoms. Weight gain was common after a year of A-ARI, and the portion of this that was expected to not fully reverse and to contribute to metabolic disease eventually caused an expected QALY loss equivalent to about 1 month of active depression in adults for whom additional weight gain is a medical risk (ie, those who were overweight at baseline). Although falls were more common with C-BUP, the expected magnitude of harms from falls was limited: a QALY loss equivalent to about half a week in adults 65–84 and a week and a half in adults 85–89.

The potentially practice-changing finding of this work is that aripiprazole augmentation was estimated to be inferior to switching to another antidepressant monotherapy for TRD in overweight adults, once metabolic harms and TD were considered. Given that aripiprazole is one of the second-generation antipsychotics with the least impact on weight and has no greater risk of TD than other second-generation

antipsychotics, these findings likely extend to other second-generation antipsychotics in TRD as well.[26,47] In recent years, up to 20% of US adults with major depressive disorder have been prescribed antipsychotics, mostly of the second-generation subclass, which translates to up to 2.2 million Americans per year.[48,49] Since 73% of US adults were overweight as of 2020,[50] with even higher rates among patients with depression,[51] our model indicates that some of the estimated 2.2 million Americans taking antipsychotics annually for depression might be better served with a switch to bupropion or possibly another antidepressant monotherapy, though individual clinical considerations might override this in some circumstances.

One surprising finding from this research is the high estimated magnitude of weight-related harms of long-term prescriptions of aripiprazole in TRD. Among patients who were already overweight, the average lifetime harms of 1 year of treatment of A-ARI via weight gain were estimated to be about as large as any depression benefit relative to S-BUP. These results are surprising because meta-analyses consistently rank aripiprazole as one of the antipsychotics with the least impact on weight, largely on the basis of short-term trials in schizophrenia populations.[47] Nonetheless, long-term studies of aripiprazole in TRD corroborate that the high frequency of weight gain in the VAST-D continuation phase was not exceptional, and the amount of weight gain per week in VAST-D continuation phase was similar to the amount of weight gain per week in meta-analyses of shorter trials.[42,43]

Limitations of the study include parameter uncertainty and uncertainty in model structure. Notably, there is a relative lack of high-quality follow-up studies of the long-term impacts of short-term changes in remitted vs unremitted depression and 1-time increases in weight. The model does not address the full range of side effects of treatment, including known side effects such as akathisia and insomnia and potential side effects under investigation such as a putative link between antipsychotic use and direct mortality risks in older adults with dementia. Moreover, individual patients may respond better or worse to treatment than the average values used in the models and may value specific health outcomes more or less than the participants from whom the utility values were derived. While the focus of this study is in TRD, some participants in VAST-D would not have met the most common definition of TRD, having failed only 1 prior antidepressant trial. Given the special populations focus of the included studies (OPTIMUM for older adults; VAST-D for veterans, generally male with high rates of comorbid PTSD), findings from the included studies may not generalize to clinical populations with different characteristics. In addition, our study does not test how these treatments compare in patients who have not yet failed at least 1 antidepressant trial. Our model only included 1 year of treatment, but many patients with TRD have recurrent depression and will need ongoing treatment, which will offer different risk and benefit profiles.

Conclusions

When VAST-D was first published, some commentators argued that antipsychotics ought to be used earlier in depression treatment, on the basis of VAST-D efficacy data.[52] One consideration missing from that discussion was an analysis of the full long-term harms of side effects of treatment. Our model addresses this gap and also incorporates data from a subsequent trial of S-BUP, C-BUP, and A-ARI. In our model, C-BUP was preferred over S-BUP and A-ARI in adults younger than 85 years with depression who did not respond to initial antidepressant treatment. Among adults with elevated BMI at baseline, A-ARI was the least preferred of the 3 treatments. To the extent that the assumptions of our model are accurate, these results suggest that providers should consider C-BUP for TRD and consider alternatives to A-ARI for TRD among adults with elevated baseline BMI. The limitations of our risk-benefit analysis emphasize the importance of shared decision-making in treatment decisions. Nonetheless, it can be challenging for patients and clinicians to accurately balance short-term benefits with insidious long-term risks, which makes this decision analysis a useful starting point for shared decision-making.

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Supplementary Material

Article Title: Aripiprazole or Bupropion Augmentation Versus Switching to Bupropion in Treatment Resistant Depression: A Risk-Benefit Analysis

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LIST OF SUPPLEMENTARY MATERIAL FOR THE ARTICLE

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This Supplementary Material has been provided by the authors as an enhancement to the published article. It has been approved by peer review; however, it has undergone neither editing nor formatting by in-house editorial staff. The material is presented in the manner supplied by the author.

Supplementary Table for "Aripiprazole or bupropion augmentation vs switching to bupropion in treatment resistant depression: A benefit-risk analysis"

The base case assumed that the discount rate is 1.5%, time horizon is lifetime, disabilities from falls last 1 year, tardive dyskinesia incidence is derived from the class-wide incidence of second generation antipsychotics, a portion of weight gain is not reversed after discontinuation, weight change is calculated as a difference across arms, and patients of non-elevated weight at baseline are unaffected by weight gain. Univariate sensitivity analyses relax these assumptions in Supplementary Table 1 below.

Supplementary Table 1: Probability of treatments being most favored under univariate sensitivity analyses

Group	PSA Favorite	B0	D3	D0	H20	F2	ATD	WR3	NBT	WA
Age: 18-64 BMI: < 25	% S-BUP	0.5	0.4	0.6	0.1	0.7	0.3	0.5	0.6	0.6
	% C-BUP	87.5	78.1	93.6	67.8	86.5	70.7	87.5	88.6	96.2
	% A-ARI	12	21.5	5.8	32.1	12.8	29	12	10.8	3.2
Age: 65-84 BMI: < 25	% S-BUP	1.8	1.4	1.9	1.6	4.3	0.8	1.8	1.7	2.2
	% C-BUP	83	79.9	86.5	81.8	72.8	62.8	83	82.6	89.9
	% A-ARI	15.2	18.7	11.6	16.6	22.9	36.4	15.2	15.7	7.9
Age: 84-89 BMI: < 25	% S-BUP	5.2	4.4	6.7	5.2	8.7	1.9	5.2	6	8.3
	% C-BUP	36	33.9	37.7	36	17.2	20.3	36	34.7	**46.5****
	% A-ARI	58.8	61.7	55.6	58.8	74.1	77.8	58.8	59.3	45.2
Age: 18-64 BMI: ≥ 25	% S-BUP	0.6	0.6	0.6	0.6	0.9	0.8	0.5	0.6	0.6
	% C-BUP	99.4	99.1	99.4	91.3	99	99.1	90.4	99	99.4
	% A-ARI	0	0.3	0	**8.1**	0.1	0.1	**9.1**	0.4	0
Age: 65-84 BMI: ≥ 25	% S-BUP	2.5	2.4	2.6	2.4	7.4	2.2	2.2	2.6	2.5
	% C-BUP	96.8	96.2	97	96.6	91.1	96	89.8	94.9	96.8
	% A-ARI	0.7	1.4	0.4	1	1.5	1.8	**8**	2.5	0.7
Age: 85-89 BMI: ≥ 25	% S-BUP	15.8	14.1	17.7	15.8	32.4	13.2	10.4	13.7	15.8
	% C-BUP	70	66.5	71.2	69.9	41.6	61.7	54.4	60.2	70
	% A-ARI	14.2	**19.4**	11.1	14.3	26	**25.1**	**35.2**	**26.1**	14.2

Legend: B0: The "base case" column lists for each of 6 patient subgroups the percent of 1000 probabilistic sensitivity analysis runs that favor each of 3 treatments. Columns D3-WA represent the same quantities for 8 different univariate sensitivity analyses. BMI: body mass index; PSA: probabilistic sensitivity analysis; S-BUP: switch to bupropion monotherapy; C-BUP: combination therapy with bupropion; A-ARI: augmentation with aripiprazole. Univariate sensitivity analyses: D3: temporal discount rate set to 3%; D0: temporal discount rate set to 0%; H20: time horizon of 20 years; F2: disabilities after falls last 2 years; ATD: tardive dyskinesia incidence is derived from agent-specific incidence for aripiprazole; WR3: antipsychotic weight gain fully reversible after 3 years; NBT: weight gain with A-ARI is defined as change from baseline; WA: weight gain can have some effects on quality of life and mortality in patients with non-elevated weight. Cells in bold represent treatment strategies that have gained in favorability rank in a given univariate sensitivity analysis compared to in the base case. **: Treatment strategies that became the most favorable in a univariate sensitivity analysis that were not the most favorable in the base case.