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Journal

The Journal of clinical psychiatry, 81(4)

ISSN

0160-6689

Authors

Mohamed, Somaia
Johnson, Gary R
Sevilimedu, Varadan
et al.

Publication Date

2020-06-01

DOI

10.4088/jcp.19m13038

Original Research

Impact of Concurrent Posttraumatic Stress Disorder on Outcomes of Antipsychotic Augmentation for Major Depressive Disorder With a Prior Failed Treatment: VAST-D Randomized Clinical Trial

Somaia Mohamed, MD, PhD[a,*]; Gary R. Johnson, MS[b]; Varadan Sevilimedu, MBBS, DrPH[b,c]; Sanjai D. Rao, MD[d]; Paul B. Hicks, MD[e]; Peijun Chen, MD, PhD, MPH[f]; Kimberly Lauro, PhD[d]; George Jurjus, MD[f]; Patricia Pilkinton, MD[g]; Lori Davis, MD[g]; James A. Wilcox, MD, PhD[h]; Ali Iranmanesh, MD[i]; Mamta Sapra, MD[i]; Muhammad Aslam, MD[j]; James Michalets, MD[k]; Michael Thase, MD[l]; and Sidney Zisook, MD[d]; for the CSP#576 VAST-D Investigators[m]

ABSTRACT

Objective: To determine whether concurrent posttraumatic stress disorder (PTSD) should affect whether to augment or switch medications when major depressive disorder (MDD) has not responded to a prior antidepressant trial.

Methods: Patients at 35 Veterans Health Administration medical centers from December 2012 to May 2015 with nonpsychotic MDD (N = 1,522) and a suboptimal response to adequate antidepressant treatment were randomly assigned to 3 "next step" treatments: switching to bupropion, augmenting the current antidepressant with bupropion, and augmenting with the antipsychotic aripiprazole. Blinded ratings with the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated ($QIDS\text{-}C_{16}$) determined remission and response by 12 weeks and relapse after remission. Survival analyses compared treatment effects in patients with concurrent PTSD diagnosed with the Mini-International Neuropsychiatric Interview (n = 717, 47.1%) and those without PTSD (n = 805, 52.9%).

Results: Patients diagnosed with PTSD showed more severe depressive symptoms at baseline and were less likely to achieve either remission or response by 12 weeks. Augmentation with aripiprazole was associated with greater likelihood of achieving response (68.4%) than switching to bupropion (57.7%) in patients with PTSD (relative risk [RR] = 1.26; 95% CI, 1.01–1.59) as well as in patients without PTSD (RR = 1.29; 95% CI, 1.05–1.97) (78.9% response with aripiprazole augmentation vs 66.9% with switching to bupropion). Treatment comparisons with the group receiving augmentation with bupropion were not significant. There was no significant interaction between treatment group and PTSD on remission ($P = .70$), response ($P = .98$), or relapse ($P = .15$).

Conclusions: Although PTSD was associated with poorer overall outcomes, the presence of concurrent PTSD among Veterans in this trial did not affect the comparative effectiveness of medications on response, remission, or relapse after initial remission.

Trial Registration: ClinicalTrials.gov identifier**:** NCT01421342

J Clin Psychiatry 2020;81(4):19m13038

To cite: Mohamed S, Johnson GR, Sevilimedu V, et al. Impact of concurrent posttraumatic stress disorder on outcomes of antipsychotic augmentation for major depressive disorder with a prior failed treatment: VAST-D randomized clinical trial. *J Clin Psychiatry*. 2020;81(4):19m13038.

To share: https://doi.org/10.4088/JCP.19m13038

[a]VA New England Mental Illness, Research, Education and Clinical Center, West Haven, Connecticut
[b]VA Connecticut Healthcare System, West Haven, Connecticut
[c]Yale University School of Public Health, New Haven, Connecticut
[d]VA San Diego Healthcare System, San Diego, California
[e]Baylor Scott and White Health, Temple, Texas
[f]Louis Stokes Cleveland VA Medical Center, Cleveland, Ohio
[g]Tuscaloosa VA Medical Center, Tuscaloosa, Alabama
[h]Tucson VA Medical Center, Tucson, Arizona
[i]Salem VA Medical Center, Salem, Virginia
[j]Cincinnati VA Medical Center, Cincinnati, Ohio
[k]Charles George VA Medical Center, Asheville, North Carolina
[l]Philadelphia VA Medical Center, Philadelphia, Pennsylvania
[m]The names of all participants in the VAST-D Study are listed in Supplementary Appendix 1.
**Corresponding author:* Somaia Mohamed, MD, PhD, VA Connecticut Healthcare System, 950 Campbell Ave, Mailstop (182), West Haven, CT 06516 (somaia.mohamed@va.gov).

Major depressive disorder (MDD) is a chronic debilitating disorder, accounting for more than half of all disability attributable to mental illness worldwide[1] with only one-third of patients experiencing remission after an initial antidepressant trial.[2,3] A recent randomized clinical trial of alternative next step treatments, the Veterans Administration (VA) Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) study,[4] recruited Veterans (N = 1,522) who had been unresponsive to previous antidepressant treatment and evaluated 3 next-step prescribing strategies. Augmentation with the antipsychotic aripiprazole resulted in a significantly greater likelihood of remission compared to switching to bupropion monotherapy during a 12-week acute treatment phase and a greater likelihood of response (greater than 50% improvement) than either switching to bupropion or augmenting previous antidepressant therapy with bupropion during a 24-week extension phase for responders.

In this sample of Veterans with MDD, co-occurring posttraumatic stress disorder (PTSD) was diagnosed in 717 (47%) of 1,522 participants, raising the question of whether PTSD may have affected the trial results.[5] A recent meta-analysis[6] suggested that antipsychotics may be effective in the treatment of PTSD, and while a previous VA trial[7] of risperidone for PTSD did not find significant effects on the primary outcome, some secondary outcomes were significant, and at least one trial[8]

Clinical Points

- It is not known whether concurrent posttraumatic disorder (PTSD) can affect the results of clinical trials of medications for major depressive disorder (MDD).
- This secondary analysis of a multisite trial of augmentation (with aripiprazole or bupropion) as compared to switching to bupropion found that Veterans with concurrent PTSD had uniformly worse outcomes than those with MDD alone.
- The relative effectiveness of 3 "next-step" strategies for MDD was not altered by the presence of concurrent PTSD. Augmentation with aripiprazole was superior to other strategies on some measures.

suggested that bupropion, in contrast, was not effective for PTSD; thus, it is possible that VAST-D results reflected the greater effectiveness of aripiprazole in the treatment of the subgroup with comorbid PTSD. A secondary analysis[9] reported one significant clinical moderator of treatment effects but did not examine PTSD.

PTSD is a common comorbidity among patients with MDD,[10] especially among war-zone Veterans with MDD,[11–13] but also among non-Veterans.[10,14] In the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[10] 17% of participants were diagnosed with comorbid PTSD, while data from the Veterans Health Administration[15] suggest that in 2012, of 309,374 Veterans with MDD without psychosis or bipolar disorder, 43% were also diagnosed with PTSD. Patients with MDD and PTSD have been found to have worse outcomes than those with MDD alone on measures of depressive symptoms, quality of life,[16] and suicidality.[11] Whether patients with MDD and PTSD show significantly greater relative benefits from an antipsychotic as compared to those without PTSD has not been evaluated. One of the distinctive features of VAST-D is that it did not exclude patients with non-psychotic comorbidities to increase the generalizability of the results.[17]

This secondary analysis of data from the VAST-D study has 3 objectives: (1) to compare baseline sociodemographic and clinical characteristics of participants with MDD alone to those with MDD and PTSD, (2) to compare outcomes between these 2 groups of patients as measured by remission and response of depressive symptoms after 12 weeks of treatment and relapse after remission, and, finally, (3) to compare the interaction of treatment and PTSD on remission, response, and relapse among Veterans with and without comorbid PTSD.

METHODS

Study Design

VAST-D (ClinicalTrials.gov identifier: NCT01421342) was a multisite randomized, single-blind, parallel-assignment trial conducted from December 2012 to May 2015 that included 1,522 Veterans Health Administration (VHA) patients who experienced suboptimal response to at least one course of antidepressant treatment meeting minimal standards for dose and duration.[17]

Patient Selection and Interventions

Participants were VHA patients, aged 18 years or older with a MDD diagnosis, who were referred by their treating VA clinicians. Eligible participants had a suboptimal response to a treatment course with a selective serotonin reuptake inhibitor (SSRI), serotonin-norepinephrine reuptake inhibitor (SNRI), or mirtazapine that met or exceeded minimal standards for dose and duration of treatment. Methodological details were published previously.[4]

Participants at 35 VA medical centers were randomly assigned in a stratified randomization scheme (1:1:1) to 1 of 3 treatment strategies: switch to another antidepressant (Switch-BUP); augment current treatment with bupropion (Aug-BUP); or augment current treatment with an antipsychotic (Aug-ARI). Dose adjustments after standard starting doses were guided by "measurement-based care."[4]

Measures

Diagnoses of comorbid PTSD were made with the Mini-International Neuropsychiatric Interview (MINI).[18] The primary outcome was remission ("close" to asymptomatic status), operationalized as a score on the 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated ($QIDS\text{-}C_{16}$)[19] ≤ 5 at 2 consecutive scheduled follow-up visits during the 12-week acute treatment phase. The $QIDS\text{-}C_{16}$ includes 16 items with a potential range of 0–27 with higher scores reflecting more severe symptoms. The $QIDS\text{-}C_{16}$ was administered at every visit. Secondary outcomes included "response," a reduction in $QIDS\text{-}C_{16}$ score from baseline by $\geq 50\%$,[20] and "relapse," defined as a $QIDS\text{-}C_{16}$ score of ≥ 11 for those participants who previously had achieved acute-phase remission. Other measures have been described previously.[4,17]

Statistical Methods

Some sociodemographic and clinical characteristics differed between participants with PTSD and without PTSD (see Table 1). Remission and response outcomes for patients with and without comorbid PTSD were compared using Cox regression models with comorbid PTSD and treatment as independent variables with an interaction term for treatment and PTSD (see Tables 2–4). Multivariable Cox regression models were developed using stepwise regression in which significant predictors of outcome that were associated with PTSD were added to the models to adjust estimates of PTSD and treatment effects for covariates. Comparisons were expressed by relative risk ratios (RRs) estimated from hazard ratios from Cox models and 95% confidence intervals (CIs), reporting the Wald test *P* values.

A set of supportive analyses examined outcomes in a survival analysis of time to remission and time to response. Kaplan-Meier plots assessed cumulative probability of remission or response over the 12-week acute phase. The

Table 1. Distribution of Baseline Characteristics by PTSD Diagnosis at Baseline

Variable	PTSD Diagnosis (by MINI Screen)[a] No (n = 805) Mean	SD	Yes (n = 717) Mean	SD	*P* Value
Age, y	55.0	12.3	53.7	12.1	.046
PHQ-9 score[b] (baseline)	15.3	5.1	17.2	5.0	< .0001
QIDS-C_{16} score[c] (baseline)	16.1	3.2	17.4	3.2	< .0001
EuroQol Health State Score[d]	55.9	20.4	51.4	20.1	< .0001
Q-LES-Q-SF QOL score[e]	42.5	13.9	38.5	14.8	< .0001
Complicated Grief score[f]	12.8	3.9	14.5	4.4	< .0001
Mixed hypomania features score[g]	11.4	2.6	12.0	2.7	< .0001
BAI score[h]	16.4	10.3	22.2	11.6	< .0001
BMI	31.6	6.9	31.9	7.4	.52
ACE Study scale score[i]	3.0	2.4	3.3	2.7	.066
Positive Mental Health score[j]	15.5	4.1	14.5	4.1	< .0001
CIRS score[k]	11.2	5.3	11.2	5.1	.94
Current episode duration,[l] mo	73.0	116.9	102.6	145.6	< .0001
Index trial duration,[m] mo	40.6	49.8	34.2	42.6	.007
	N	**%**	**N**	**%**	
Sex (male)	675	83.9	621	86.6	.13
Marital status					
Married/cohabitating/civil commitment	348	43.2	342	47.4	.16
Divorced	302	37.5	265	37.0	
Never married	123	15.3	85	11.9	
Widowed	32	4.0	25	3.5	
Ethnicity					.0004
Hispanic	62	7.7	95	13.2	
Race					< .0001
White	577	71.7	440	61.4	
Black	166	20.6	201	28.0	
Other	62	7.7	76	10.6	
Employment status[n]					.53
Employed	217	27.0	170	23.7	
Retired (not working)	245	30.4	229	31.9	
Unemployed (includes disability or on assistance)	339	42.1	315	43.9	
CGI-S score[o]					< .0001
Borderline mentally ill	4	0.5	1	0.1	
Mildly ill	68	8.4	25	3.5	
Moderately ill	392	48.7	263	36.7	
Markedly ill	248	30.8	259	36.1	
Severely ill	77	9.6	134	18.7	
BAS score[p]					< .025
Absent	601	74.7	482	67.2	
Questionable	144	17.9	170	23.7	
Mild akathisia	47	5.8	45	6.3	
Moderate akathisia	11	1.4	18	2.5	
Marked akathisia	1	0.1	1	0.1	
Severe akathisia	1	0.1	0	0.0	
Suicidal ideation (CSSR-S[q,r])					
Lifetime history					
Wishing to be dead	527	65.8	515	73.8	.0008
No specific thoughts	407	49.2	399	42.8	.014
Active SI without a plan	321	77.7	327	80.5	.32
Active SI with some intent	238	57.8	227	55.9	.59
Active SI with specific plan	189	54.1	175	56.9	.43
Recent history (last 3 mo)					
Wishing to be dead	263	34.1	297	44.2	< .0001
No specific thoughts	117	15.4	141	21.2	.005
Active SI without a plan	81	64.3	106	70.7	.26
Active SI with some intent	23	18.4	38	25.5	.16
Active SI with specific plan	17	13.6	23	15.4	.67

[a]Diagnosis of PTSD determined from MINI interview prior to randomization.

[b]Patient Health Questionnaire (PHQ-9): range, 0 (better) to 27 (worse); see http://www.apa.org/pi/about/publications/caregivers/practice-settings/assessment/tools/patient-health.aspx.

[c]Quick Inventory of Depressive Symptomatology (QIDS-C_{16}): range, 0 (better) to 27 (worse); see www.ids-qids.org.

[d]EuroQol Health State Score from the EQ-5D: range, 0 (worst imaginable) to 100 (best imaginable); see http://www.euroqol.org/.

[e]14-Item Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form (Q-LES-Q-SF) score: range, 14 (worst) to 70 (best); see Endicott et al.[21]

[f]Complicated Grief score = study-specific questionnaire assessing grief (range, 7 [best] to 21 [worst]).

[g]Mixed hypomania features score (*DSM* criteria), from a study-specific questionnaire with 9 elements: range, 9 (best) to 27 worst).

[h]Beck Anxiety Inventory (BAI): range, 0 to 63; see https://www.beckinstitute.org/get-informed/tools-and-resources/professionals/patient-assessment-tools/.

[i]Adverse Childhood Experiences (ACE) Study scale: range, 0 (no experiences endorsed) to 10 (all experiences endorsed); see https://www.goodtherapy.org/blog/psychpedia/ace-questionnaire

[j]Positive Mental Health score, from a study-specific questionnaire assessing positive aspects of mental health: range, 6 (worst) to 28 (best).

[k]Cumulative Illness Rating Scale (CIRS) score: range, 0 (best) to 56 (worst); see http://www.sciencedirect.com/science/article/pii/S0895435606002873.

[l]Current episode duration = duration (mo) of current episode of depression at time of enrollment.

[m]Index trial duration = duration (mo) of the current episode of antidepressant treatment trial at the time of evaluation for eligibility.

[n]There were 7 patients with missing employment status (3 with PTSD and 4 with no PTSD).

[o]Clinical Global Impressions–Severity of Illness scale (CGI-S) score: range, 1 (less severe) to 7 (more severe); see https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2880930/.

[p]Barnes Akathisia Scale (BAS) severity of drug-related akathisia: range, 0 (absent) to 5 (severe); see Barnes.[22]

[q]Columbia Suicide Severity Rating Scale (CSSR-S) risk assessment of suicidal ideation: range, 0 (best—no ideation) to 5 (worst—active SI with specific plan); see http://cssrs.columbia.edu/the-columbia-scale-c-ssrs/about-the-scale/.

[r]CSSR-S data were missing for some participants, resulting in smaller denominators: Lifetime history: total n=698 for PTSD and 801 for non-PTSD; Recent history: total n=672 for PTSD and 771 for non-PTSD. Questions about active SI were assessed for only those with active thoughts according to CSSR-S interview script.

Abbreviations: BMI = body mass index, MINI = Mini-International Neuropsychiatric Interview, PTSD = posttraumatic stress disorder, QOL = quality of life, SI = suicidal ideation.

analysis of repeated QIDS-C_{16} scores was conducted using mixed-effects repeated-measures models to compare overall treatment effects and changes in QIDS-C_{16} score over the 12-week acute phase and assess treatment by PTSD and treatment by time interactions on QIDS-C_{16} trajectories (Supplementary Appendix 2 and Supplementary Table 1). SAS software version 9.4 (2018; SAS Institute Inc; Cary, North Carolina) was used to complete these analyses.

The VA Office of Research and Development and VA Central Institutional Review Board (CIRB) approved the study, and the National Institutes of Health provided a certificate of confidentiality. The CIRB conducted annual

Table 2. Relative Risk of Remission and Response for Participants With PTSD Versus Participants Without PTSD by Treatment Group and for the Whole Cohort (Univariable and Multivariable Models)[a]

	Remission						Response					
	Remission, %		Univariable (PTSD)		Multivariable		Response (%)		Univariable (PTSD)		Multivariable	
Treatment Group	PTSD	No PTSD	RR[b]	95% CI[c]	Adjusted RR[d]	95% CI[c]	PTSD, %	No PTSD, %	RR[b]	95% CI[c]	Adjusted RR[d]	95% CI[c]
Switch-BUP (n = 511)	15.7	28.5	0.498	0.338–0.733	0.698	0.468–1.04	57.7	66.9	0.762	0.611–0.951	0.882	0.702–1.107
Aug-BUP (n = 506)	20.5	32.8	0.596	0.421–0.845	0.759	0.532–1.08	61.1	69.8	0.739	0.595–0.918	0.842	0.674–1.05
Aug-ARI (n = 505)	22.7	33.9	0.611	0.434–0.858	0.836	0.592–1.18	68.4	78.9	0.749	0.610–0.920	0.861	0.695–1.06
Whole cohort (N = 1,522)	19.5	31.8	0.567	0.462–0.697	0.769	0.620–0.953	47.1	72.1	0.745	0.658–0.843	0.860	0.755–0.979

[a]There were no significant interactions between treatment and PTSD on outcomes. Remission and response were significantly greater for participants without PTSD than those with PTSD overall and within each treatment group.
[b]RR of outcome for PTSD/No PTSD. An RR value < 1.0 indicates lower outcome rate in the PTSD group. RR was determined from estimated hazard ratio HR from Cox regression models.
[c]95% CIs for estimated RR of outcome for PTSD/No PTSD.
[d]The adjusted RRs were from multivariable models for remission and response (n = 1,498 participants with all assessments) and included treatment, PTSD status, and scores from baseline assessments: QIDS-C_{16}, Q-LES-Q-SF quality of life subscale, BAI, duration of index treatment trial (mo; log transformed), duration of current episode of depression (mo; log transformed), and EuroQOL thermometer scale.
Abbreviations: Aug-ARI = augmentation with aripiprazole, Aug-BUP = augmentation with bupropion, BAI = Beck Anxiety Inventory, PTSD = posttraumatic stress disorder, QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated, Q-LES-Q-SF = 14-item Quality of Life Enjoyment and Satisfaction Questionnaire-Short Form, RR = risk ratio, Switch-BUP = switch to bupropion.

continuing review, and a Data Monitoring Committee reviewed the study biannually. All participants provided written informed consent and privacy authorization.

RESULTS

Baseline Symptoms and Quality of Life and Trauma Exposure

Comparison of participants diagnosed with and without concurrent PTSD showed a greater proportion of African Americans and Hispanic individuals in the PTSD group, and that participants with comorbid PTSD had more severe depressive symptoms on QIDS-C_{16} and the Patient Health Questionnaire-9 (PHQ-9)[23] scales, as well as Clinical Global Impressions–Severity of Illness scale scores[24] denoting greater severity of illness (Table 1). Participants with PTSD also had more severe symptoms on measures of complicated grief, mania/hypomania, and anxiety as well as a more prolonged duration of the current episode of depression (Table 1). On 2 measures of quality of life (the EuroQol Health State Score from the EQ-5D[25] and the quality of life subscale of the 14-item Quality of Life Enjoyment and Satisfaction-Short Form [Q-LES-Q-SF][21]), Veterans diagnosed with PTSD had significantly lower scores (Table 1).

Among a subgroup of Veterans diagnosed with PTSD who were assessed with the PTSD Check List (PCL-5),[26,27] the primary trauma involved combat-related events for 46.1% and other military service–related events for 36.6%. A total of 89.9% reported that the traumatic event involved either an actual death or a perceived threat of death.

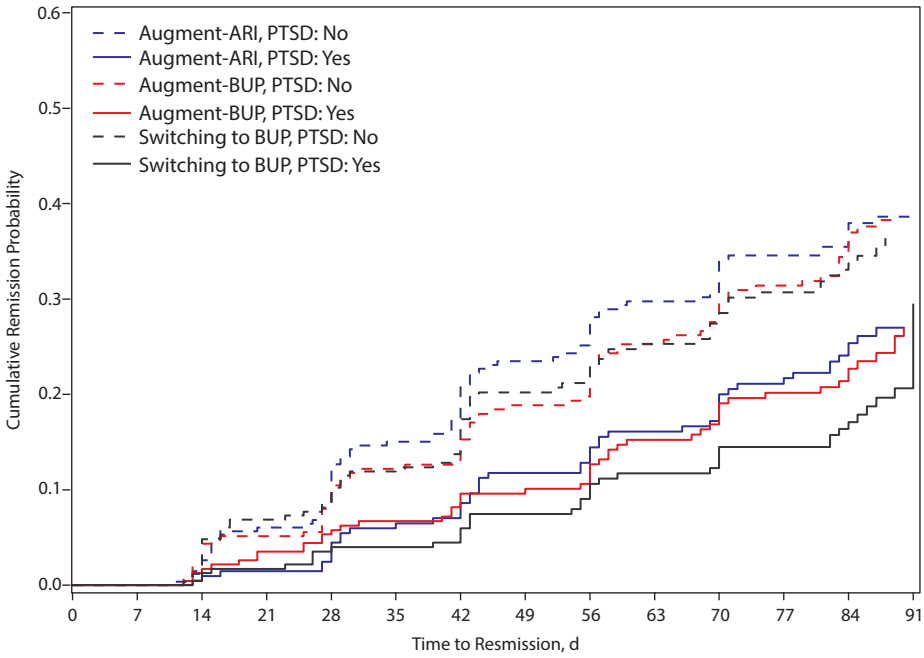
Retention

Of the 717 participants with PTSD, 198 (27.6%) were withdrawn from the study prior to week 12 compared to 187 (23.2%) of 805 participants without PTSD (difference = 4.4% [95% CI, 0.001%–8.76%], $P = .0495$). The difference in withdrawals for those with PTSD versus those without PTSD was greatest in the Aug-BUP group (29.5% vs 21.4%, respectively; difference = 8.1% [95% CI, 0.52%–15.7%], $P = .035$) but similar in the Switch-BUP and Aug-ARI groups (Supplementary Table 2). Of the withdrawals in both groups, participants in the PTSD group were less likely to be withdrawn due to a side effect (24.8%) compared to those without PTSD (36.9%), (difference = 12.1% [95% CI, 2.9%–21.3%], $P < .05$).

Remission, Response, and Relapse Among Veterans With and Without PTSD

There was a 43% lower risk of remission within 12 weeks of initiating treatment among Veterans with comorbid PTSD compared to those without PTSD with an overall risk ratio that is significantly less than 1.0 overall (risk ratio [RR] = 0.567; 95% CI, 0.462–0.697) and also for each of the 3 treatments (Table 2). The relative effect of PTSD remained significantly associated with lower remission when multivariable regression models on the whole cohort included severity of depression (by QIDS-C_{16} score) and other significant baseline measures (RR = 0.769; 95% CI, 0.620–0.953). However, within–treatment group comparisons were not significant (Table 2). Kaplan-Meier plots of cumulative probability of remission for each treatment group by PTSD status show that remission rates are distinctly lower in the PTSD group and that the Switch-BUP treatment group had the lowest rate of remission (Figure 1). Relative risk of response was also significant for those with PTSD overall (RR = 0.745; 95% CI, 0.658–0.843) and for each of the 3 treatments, reflecting a 25% lower symptom improvement among Veterans with PTSD. For relapse after remission in the acute phase, the risk of relapse was not significantly greater among the participants with PTSD (RR = 1.30; 95%

Figure 1. Cumulative Probability of Remission in the Acute Phase by PTSD Status and Treatment Group[a]



[a]Plots are of cumulative probability of remission for each treatment group within the PTSD and no PTSD strata. Plot is truncated at 91 days for the end of assessments in the acute treatment phase.
Abbreviations: ARI = aripiprazole, BUP = bupropion, PTSD = posttraumatic stress disorder.

Table 3. Relative Risk of Relapse for Participants With PTSD vs Participants Without PTSD by Treatment Group and for the Whole Cohort (Univariable and Multivariable Models)[a]

	Relapse Among Remitters					
	Relapse,[b]		Univariable (PTSD)		Multivariable	
Treatment Group	PTSD	No PTSD	RR[c]	95% CI[d]	Adjusted RR[e]	95% CI[d]
Switch-BUP (n = 114)	25.6	21.3	1.11	0.502–2.44	0.95	0.426–2.10
Aug-BUP (n = 136)	36.0	19.8	2.19	1.13–4.25	1.78	0.905–3.50
Aug-ARI (n = 146)	23.5	26.3	0.87	0.436–1.73	0.82	0.426–1.64
Whole cohort (n = 396)	28.6	22.7	1.30	0.867–1.94	1.13	0.746–1.70

[a]There were no significant interactions between treatment and PTSD on outcomes.
[b]Relapse rate was calculated among those participants (n = 396) who remitted during the acute treatment phase; relapse was defined as a worsening in QIDS-C_{16} score ≥ 11 after remission during up to 36 weeks of follow-up.[4] Relapse rate for Aug-BUP was significantly greater in the PTSD group (RR = 2.19, $P < .05$). Other comparisons for relapse within treatment groups were not significant.
[e]The adjusted RRs were from multivariable model for relapse (n = 396 participants with all assessments) and included the following covariables: treatment, PTSD status, and baseline assessments including QIDS-C_{16}, duration of index treatment trial (mo; log transformed), and presence of akathisia at baseline by the Barnes Akathisia Scale (absent [0] vs questionable [1] to severe [5]).
[c]RR of outcome for PTSD/No PTSD. An RR value < 1.0 = indicates lower outcome rate in the PTSD group. RR was determined from estimated hazard ratio from Cox regression models.
[d]95% CIs for estimated relative risk of outcome for PTSD/No PTSD.
Abbreviations: Aug-ARI = augmentation with aripiprazole, Aug-BUP = augmentation with bupropion, PTSD = posttraumatic stress disorder, QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated, RR = risk ratio, Switch-BUP = switch to bupropion.

CI, 0.867–1.94) (Table 3). The results across treatment groups were mixed, with significantly greater likelihood of relapse among participants with PTSD in the Aug-BUP group (RR = 2.19; 95% CI, 1.13–4.25) but not among those in the Switch-BUP or Aug-ARI groups.

Do Treatment Effects Vary With and Without Concurrent PTSD?

Comparison of the magnitude of treatment effects between pairs of treatments (risk ratios reflecting comparative effectiveness of paired treatments) among Veterans with and without PTSD showed no significant differences in comparative treatment effectiveness on remission between Veterans with and without PTSD (Table 4). For example, comparison of Aug-ARI and Switch-BUP showed risk ratios, albeit with nonsignificant effects, favoring Aug-ARI for both Veterans with PTSD (RR = 1.40; 95% CI, 0.93–2.13) and Veterans without PTSD (RR = 1.14; 95% CI, 0.84–1.55). Neither of these treatment comparisons showed significant differences, and the interaction of treatment group by PTSD stratum was also not significant ($P = .70$).

In the analysis of response, in contrast, augmentation with aripiprazole was associated with significantly greater likelihood of achieving response (68.4%) than switching to bupropion (57.7%) in patients with PTSD (HR = 1.26; 95% CI, 1.01–1.59) and also in depressed patients without PTSD (HR = 1.29; 95% CI, 1.05–1.57) (78.9% response with augment with aripiprazole vs 66.9% response with switching to bupropion) (Table 4). Here, too, the interaction of

Table 4. Treatment Effects for Study Outcomes for Participants With PTSD and Without PTSD

Outcome	PTSD		No PTSD		*P* Value
Remission					
Relative Treatment Comparison	RR[a]	95% CI[b]	RR[a]	95% CI[b]	
Aug-ARI vs Switch-BUP	1.40	0.93–2.13	1.14	0.84–1.55	
Aug-BUP vs Switch-BUP	1.29	0.85–1.96	1.08	0.79–1.47	
Aug-ARI vs Aug-BUP	1.09	0.74–1.61	1.06	0.79–1.42	
Overall treatment × PTSD interaction					.70
Response (≥ 50% Reduction)[c]					
Relative Treatment Comparison	RR	95% CI	RR	95% CI	
Aug-ARI vs Switch-BUP	1.26	1.01–1.59	1.29	1.05–1.57	
Aug-BUP vs Switch-BUP	1.04	0.83–1.31	1.07	0.87–1.32	
Aug-ARI vs Aug-BUP	1.22	0.97–1.53	1.20	0.99–1.46	
Overall treatment × PTSD interaction					.98
Relapse Among Remitters[d]					
Relative Treatment Comparison	RR	95% CI	RR	95% CI	
Aug-ARI vs Switch-BUP	0.99	0.43–2.28	1.26	0.67–2.35	
Aug-BUP vs Switch-BUP	1.68	0.77–3.64	0.85	0.43–1.68	
Aug-ARI vs Aug-BUP	0.59	0.28–1.22	1.48	0.80–2.74	
Overall treatment × PTSD interaction					.15

[a]RR was determined from hazard ratio estimates from Cox regression models including Treatment and PTSD status and interaction terms for treatment × PTSD status interaction as covariables. There was no significant interaction between treatment and PTSD.
[b]95% CIs for estimated relative risk of outcome for treatment comparisons within the PTSD and no PTSD groups.
[c]Aug-ARI vs Switch-BUP RRs were significantly greater than 1.0 at a significance level of .05 for response (> 50%) for both PTSD and No PTSD.
[d]Relapse rate was calculated among those participants (n = 396) who remitted during the acute treatment phase; relapse was defined as a worsening in QIDS-C_{16} score ≥ 11 after remission during up to 36 weeks of follow-up (4).
Abbreviations: Aug-ARI = augmentation with aripiprazole, Aug-BUP = augmentation with bupropion, PTSD = posttraumatic stress disorder, QIDS-C_{16} = 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated, RR = risk ratio, Switch-BUP = switch to bupropion.

treatment group with PTSD stratum on response was not significant ($P = .98$). There were no significant differences in response between augmentation with aripiprazole and augmentation with bupropion in either patients with PTSD or patients not diagnosed with PTSD.

The analysis of relapse showed no significant differences between pairs of treatment groups with or without PTSD and no significant interaction of treatment group and PTSD diagnosis ($P = .15$).

Finally, a repeated-measures model with QIDS-C_{16} score as the response variable and several covariates including treatment group, baseline QIDS-C_{16} score, week of visit (log transformation), interaction between treatment and week of visit, and interactions between PTSD status and treatment showed a significant difference favoring Aug-ARI as compared to Switch-BUP ($P = .045$) for the PTSD group (Figure 2B) and a similarly significant effect for those without PTSD ($P = .026$) (Figure 2A), but no significant differences for either of the other paired treatment comparisons for those with PTSD or for those without PTSD. The trend in QIDS-C_{16} scores over time showed a decline in symptoms (improvement) with time for both those with PTSD and those without PTSD ($P < .001$). Participants without PTSD had significantly lower mean QIDS-C_{16} scores than participants with PTSD ($P < .05$). However, none of the interaction terms was significant. (Supplementary Table 1). A comparison of least squares means (Supplementary Table 3) between the Aug-ARI group and the Switch-BUP group shows similar patterns as described before and observed in Table 4. That is, the least squares means of QIDS-C_{16} scores are significantly lower (ie, there is more improvement in depressive symptoms) in the Aug-ARI group as compared to the Switch-BUP group, irrespective of PTSD status. The differences in least squares means of QIDS-C_{16} scores between other treatment groups were not significant ($P > .05$).

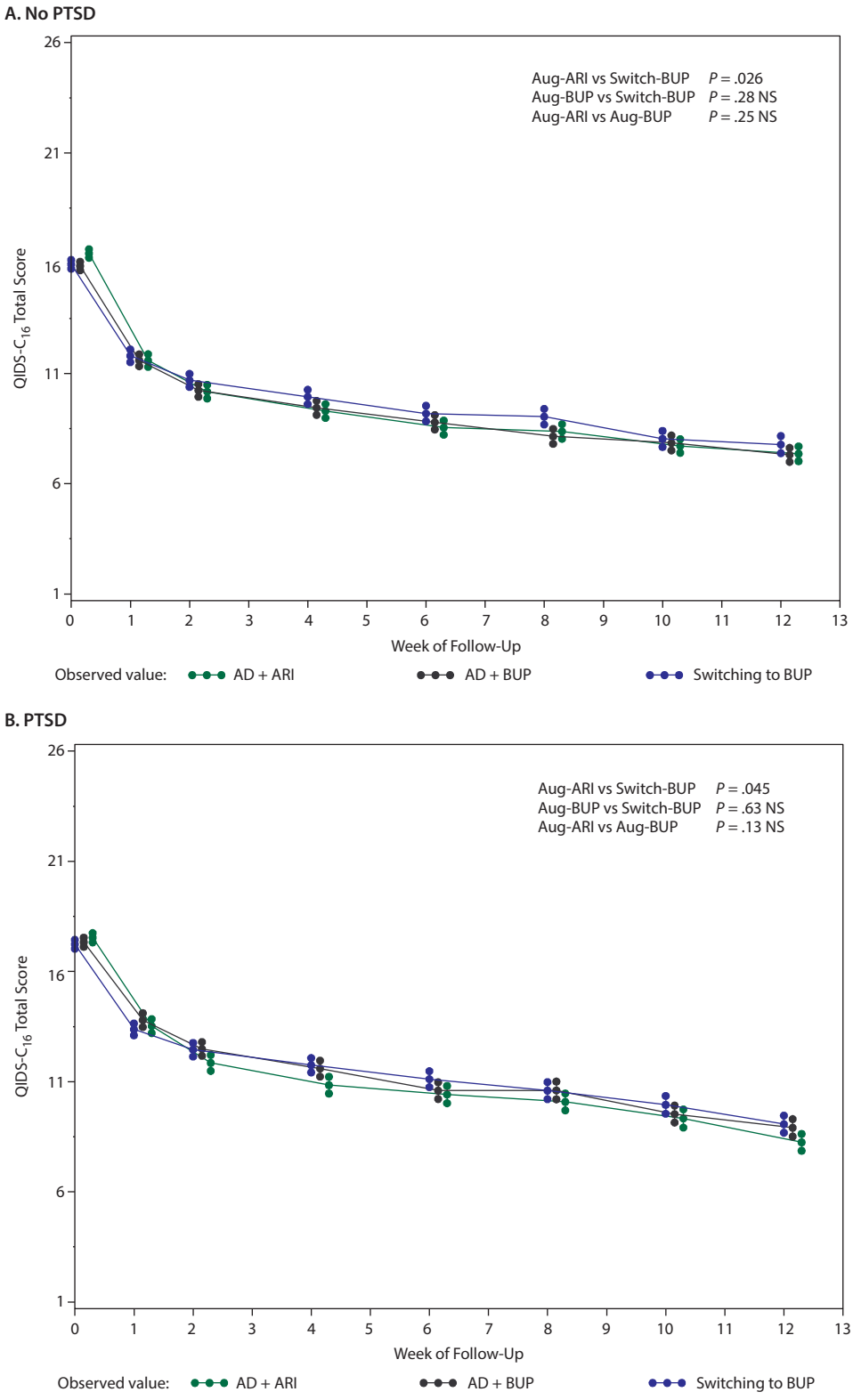
DISCUSSION

Efficacy trials of psychotropic medication have generally excluded comorbidities to allow evaluation of the impact of treatment on specific, uncomplicated mental illnesses. To increase the generalizability of treatment trials, effectiveness studies increasingly minimize diagnostic exclusions.[17] VAST-D, thus, did not exclude patients with nonpsychotic psychiatric comorbidities, and a substantial proportion had concurrent PTSD. To our knowledge, no study has previously evaluated the potentially biasing impact of PTSD on pharmacologic treatment results of patients with MDD, in part because there is rarely an adequate sample size to support secondary analyses of diagnostic subgroups in randomized trials. With a 47.1% rate of concurrent PTSD, VAST-D provided a unique opportunity to evaluate the possible impact of this concurrent disorder on the results of a randomized medication trial with blinded assessments. The fact that previous studies[5,6] had suggested that one of the treatments in VAST-D, augmentation of antidepressant treatment with the antipsychotic aripiprazole, might itself be an effective therapy for PTSD makes evaluation of the potential biasing impact of this concurrent disorder especially compelling.

The analyses presented here clearly show that Veterans with comorbid PTSD had not only more severe symptoms of depression but also more grief and anxiety at the time of study entry, and poorer quality of life. In addition, they had significantly lower likelihood of achieving both remission and response of MDD symptoms during the acute phase of the trial. Findings for relapse were mixed, with the only significant effect showing greater likelihood of relapse for patients diagnosed with PTSD among those treated with Aug-BUP. In all of these analyses there were no significant interactions between treatment group and PTSD status in the Cox regression analyses or mixed model analysis of symptom severity, showing the relative effectiveness of the 3 treatments was no different among Veterans with and without PTSD. Thus, none of our findings suggest that study conclusions regarding next-step pharmacologic treatment in VAST-D were biased by differential effectiveness of Aug-ARI on concurrent PTSD as compared to the other treatment arms.

It is notable that while in primary analyses of VAST-D,[4] Aug-ARI was significantly more likely to

Figure 2. Distribution of QIDS-C_{16} Scores During the Acute Phase by PTSD Status and Treatment Group in Patients (A) Without PTSD and (B) With PTSD[a]



[a]Plots are of mean QIDS-C_{16} scores for available observed assessments at scheduled visits during the 12-week acute treatment phase. *P* values for treatment comparisons are from repeated-measures models using general estimating equations (GEE) for QIDS-C_{16} score trajectories adjusted for treatment group and PTSD status and treatment by time interactions.

Abbreviations: AD = antidepressant, Aug-ARI = augmentation with aripiprazole, Aug-BUP = augmentation with bupropion, NS = not significant, PTSD = posttraumatic stress disorder, QIDS-SC_{16} = 16-item Quick Inventory of Depressive Symptomatology–Clinician Rated, Switch-BUP = switch to bupropion.

result in remission than Switch-BUP and Aug-ARI was more likely to lead to response than both Switch-BUP and Aug-BUP, in the PTSD subgroup analyses presented here, the only significant outcome finding was that Aug-ARI was more likely to lead to response than Switch-BUP. This attenuated result most likely reflects the reduction in sample sizes and loss of statistical power when the full sample was stratified by PTSD status.

Although the interaction terms were not statistically significant, we recognize that the magnitude of the relative difference in treatment effect of aripiprazole on remission, when compared to the Switch-BUP arm, was greater for the PTSD group (RR = 1.40) than for the group without PTSD (RR = 1.14). However, this greater effectiveness of aripiprazole for patients with PTSD is more reflective of the poorer performance of the Switch-BUP group (15.7% remission rate; see Table 2) than of a much better performance of Aug-ARI in patients with PTSD (22.7%), and thus the hypothesis that the overall treatment effect favoring Aug-ARI may have been driven by a large PTSD cohort is not consistent with the results of this study.

The secondary analysis presented here represents an important step forward for the developing field of multimorbidity—a field that has received increasing attention in both mental health and general medical research.[28–30] Multimorbidity is defined broadly as the occurrence of two or more chronic mental and/or medical conditions affecting the same individual at the same time and highlights the clinical reality that most patients do not present with a single "primary" diagnosis but rather with a tapestry of several diagnoses. A recent study[31] of VHA patients receiving outpatient mental health care showed that 77.6% had more than one mental health diagnosis. Furthermore, a review of the PTSD trial literature,[32] in contrast, showed that the vast majority of RCTs (72%) excluded comorbid substance use disorders and a comparable proportion (75%) also excluded specific psychiatric disorders. Although we are not aware of any comparable reviews of the trial literature on MDD, a recent study[33,34] examining generalizability of findings from studies of both pharmacologic and psychotherapeutic treatments for PTSD found that 60%–70% of individuals with PTSD would have been excluded from these trials. VAST-D is the first randomized trial of next-step pharmacotherapy to our knowledge that directly allows evaluation of the potential impact of PTSD multimorbidity on the comparative effectiveness of MDD treatments and thus reflects a kind of secondary analysis that will be increasingly important in the interpretation of psychiatric effectiveness trials in the presence of potentially biasing concurrent disorders and comorbidities.

Several methodological limitations require comment. First, only one antidepressant (bupropion sustained-release) and one antipsychotic (aripiprazole) were evaluated, and the generalizability of the results to other medications or to electroconvulsive therapy was not addressed in this study. Second, only 1,137 patients (74.7%) completed the 12-week acute phase, and differences in outcomes between groups, especially in these subgroup analyses, were small in magnitude. Third, it is possible that discontinuation in the group that switched to bupropion was increased by withdrawal symptoms from their previous treatment, putting that treatment alternative at a disadvantage. Fourth, the study was conducted with VA patients with several exclusion criteria. As a result, the generalizability of results from this older, predominately male population that includes a large numbers of combat Veterans is also unknown.

Finally, due to the smaller sample sizes in the PTSD and non-PTSD subgroups, some significant findings from the original trial report were not replicated.

CONCLUSION

In a VHA population of predominantly older men with nonpsychotic MDD unresponsive to antidepressant treatment, patients with comorbid PTSD showed significantly lower remission and response with 3 next-step treatments than those without PTSD. Augmentation with aripiprazole resulted in a statistically significant but small increase in the likelihood of response during 12 weeks of treatment compared with switching to bupropion monotherapy in both PTSD and non-PTSD subgroups. There were no significant interactions of PTSD diagnosis and treatment on other study outcomes.

Submitted: August 5, 2019; accepted January 2, 2020.

Published online: June 23, 2020.

Author contributions: Mr Johnson and Dr Sevilimedu had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All information and materials in the article are original.

Potential conflicts of interest: **Mr Johnson** reports his spouse was an employee of and owns stock in Bristol-Myers Squibb. **Dr Rao** is on the speaker's bureau of Janssen, Alkermes, Sunovion, and Otsuka-America and has consulted for Janssen and Alkermes. **Dr Davis** has been a consultant for Tonix, Otsuka, Lundbeck, and Janssen and has done funded research for Tonix, Otsuka, and Alkermes. **Dr Thase** reports no conflicts of interest specifically related to this research; prior to 2011, he was a consultant and speaker for and received research support from Bristol-Myers Squibb (aripiprazole) and GlaxoSmithKline (bupropion); in the past 3 years, he reports being an advisory/consultant for Acadia, Akili, Alkermes, Allergan (Forest, Naurex), Boehringer-Ingelheim, Clexio Biosciences, H. Lundbeck, Jazz, Janssen (Johnson & Johnson), Otsuka, Perception Neuroscience, Sage, Seelos and Takeda; has received grant support from Acadia, Allergan (Forest, Naurex), Axsome, Intra-Cellular, Johnson & Johnson (Janssen), Otsuka, and Takeda; has received royalties from American Psychiatric Press Incorporated, Guilford Publications, Herald House, and W. W. Norton & Company, Inc; and reports that his spouse is employed by Peloton Advantage, which does business with a number of pharmaceutical companies. **Dr Zisook** has consulted to Defender Pharmaceuticals and receives research support from COMPASS Pathways. **Drs Mohamed**, **Sevilimedu**, **Hicks**, **Chen**, **Lauro**, **Jurjus**, **Pilkinton**, **Wilcox**, **Iranmanesh**, **Sapra**, **Aslam**, and **Michalets** all report no conflicts of interest.

Funding/support: This study was supported by the Cooperative Studies Program, Department of Veterans Affairs, Office of Research and Development. Bristol Myers Squibb provided aripiprazole (Abilify) for use in this study.

Role of the sponsor: The Cooperative Studies Program, Department of Veterans Affairs, Office of Research and Development participated in the design and oversaw the conduct of the study including data collection and management and analysis.

Disclaimer: Opinions expressed herein are those of the individual authors and the contents do not represent views of the Department of Veterans Affairs or the United States Government.

Supplementary material: Available at PSYCHIATRIST.COM.

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Supplementary Material

Article Title: Impact of Concurrent Posttraumatic Stress Disorder on Outcomes of Antipsychotic Augmentation for Major Depressive Disorder With a Prior Failed Treatment: VAST-D Randomized Clinical Trial

Author(s): Somaia Mohamed, MD, PhD; Gary R. Johnson, MS; Varadan Sevilimedu, MBBS, DrPH; Sanjai D. Rao, MD; Paul B. Hicks, MD; Peijun Chen, MD, PhD, MPH; Kimberly Lauro, PhD; George Jurjus, MD; Patricia Pilkinton, MD; Lori Davis, MD; James A. Wilcox, MD, PhD; Ali Iranmanesh, MD; Mamta Sapra, MD; Muhammad Aslam, MD; James Michalets, MD; Michael Thase, MD; and Sidney Zisook, MD; for the CSP#576 VAST-D Investigators

DOI Number: https://doi.org/10.4088/JCP.19m13038

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Disclaimer

This Supplementary Material has been provided by the author(s) 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.

Appendix 1: VAST-D Study Group

The following persons participated in the VAST-D Study:

Planning Committee – S. Mohamed (Co-Chair), S. Zisook (Co-Chair), K. Biswas, M. Gerrity, T.C. Gleason, P. Guarino, G.R. Johnson, A. Kilbourne, B. Lebowitz, S. Marder, J.E. Vertrees, J. Yoon;

Executive Committee – S. Mohamed (Co-Chair), S. Zisook (Co-Chair), P. Chen, L.L. Davis, T.C. Gleason, P. Guarino, G.R. Johnson, P.B. Hicks, J.E. Vertrees, J. Yoon;

Data Monitoring Committee – S.R. Wisniewski (Chair), S. Arndt, P.J. Clayton, I.A. Cook, I.D. Glick, A. Miller;

VA Site Investigators – Albuquerque, NM: G. Villarreal; American Lake/Tacoma, WA: A. Tapp, K.A. Jones; Asheville, NC: J.P. Michalets; Atlanta, GA: A. Fareed; Baltimore, MD: B.A. Fischer, D.J. Loreck; Cincinnati, OH: M. Aslam, Clarksburg, WV: M.S. Finkel; Cleveland, OH: G. Jurjus, P. Chen; Denver, CO: T. Beresford; Hines, IL: G. Khatkhate, S. Marri, V. Davis; Indianapolis, IN: A.R. Mayeda, A.B. Niculescu, III; Kansas City, MO: K.D. Anderson; Loma Linda, CA: R. Fernando; Long Beach, CA: L.J. Albers; Madison, WI: T.M. Juergens; Memphis, TN: C.S. Nasdahl; Miami, FL: C.A. Nogues; Milwaukee, WI: G. Larson, W.G. Anderson, M. Klatt; Minneapolis, MN: J. Westermeyer, G. Yoon; Omaha, NE: S. Ramaswamy; Palo Alto, CA: T. Suppes; Philadelphia, PA: K.R. Connolly, M.E. Thase; Phoenix, AZ: C.J. Carrera, S.I. Thompson; Pittsburgh, PA: J. Kasckow; Salem, VA: A. Iranmanesh, M. Sapra; Salisbury, NC: R. Hurley, J. LaMotte; San Diego, CA: S.D. Rao; San Francisco, CA: N. Rosenlicht, S. Lieske; St. Louis, MO: D.M. Svrakic, P.J. Lustman; Tampa, FL: J.L. Winston; Temple, TX: S.S. Williams, P.B. Hicks; Tucson, AZ: J.A. Wilcox; Tuscaloosa, AL: P.D. Pilkinton, L.L. Davis; Washington, DC: J.T. Little; West Haven, CT: D.C. D'Souza;

VA Site Sub-Investigators – Albuquerque, NM: J. Carty, J. Canive, G. Toney; American Lake/Tacoma, WA: D. Agrawal, N. Klizieh, L. Lyon; Asheville, NC: J. Farmer, E. Makela, J. Nicholls; Atlanta, GA: J. Will, K. Salles-Shahid; Baltimore, MD: R. Buchanan, C. Harrison-Restelli, S. Himelhoch; Cincinnati, OH: E. Nelson, D.M. Beal; Clarksburg, WV: P. Sullivan, J. Vogt; Cleveland, OH: M. Ignatowski; Denver, CO: M. Wasserstein, N. Wongngamnit; Hines, IL: n/a; Indianapolis, IN: H. Bhagar; Kansas City, MO: T. Demark; Loma Linda, CA: V.G. Bhat, A. Mihas, A. Hayton; Long Beach, CA: C. Reist, C. Nguyen; Madison, WI: E. Ahearn, D. Krahn, K. Dutra; Memphis, TN: K.D. Clark, K. Sakauye; Miami, FL: M. Trujillo; Milwaukee, WI: D. Cory; Minneapolis, MN: P.J. Dickmann, M. Warwick; Omaha, NE: M. Amani, S. Bhatia, J. Dickson, V. Kolli, V. Monga, J. Madabushi, F. Petty; Palo Alto, CA: R. Bongale, B. Bregman, M. Castelli, M. Ostacher, D. Ravindranath, H. Hsin, V. Cosgrove, S. Miller; Philadelphia, PA: D. Oslin, E. Volfson; Phoenix, AZ: n/a; Pittsburgh, PA: S. Forman; Salem, VA: n/a; Salisbury, NC: M. Dalsania, C. Lamar, R. Vaidya; San Diego, CA: A. Iglewicz, H. Thorisdottir; San Francisco, CA: N. Majumdar; St. Louis, MO: A.L. Taylor, J. Mathews; Tampa, FL: M. Warren; Temple, TX: P.J. Pazzaglia, K. Rivera; Tucson, AZ: D. Emelity; Tuscaloosa, AL: S. Sloupe; Washington, DC: R.R. Peebles, X. Shao, V. Holder-Perkins, M.D. Llorente; West Haven, CT: J.

Cahill, A. Gupta, S. Gupta, E.A. Likins-Graham, M. Ranganathan, G. Yoon, J. Carlson, D. Boggs, R.A. Sewell;

VA Site Coordinators – Albuquerque, NM: L.A. Calais, M. Lackey, A. Mank, L. Adamson, B. Portillo; American Lake/Tacoma, WA: S. Hunt, K. Miller, S. Devroy; Asheville, NC: A. Weiss, W. Sprinkle; Atlanta, GA: L. Britan-Lang; Baltimore, MD: W.L. Williams; Cincinnati, OH: J. Bunke, J. Randolph; Clarksburg, WV: D. Shriver, M. Shuttleworth, E. Cox, D. Goldizen; Cleveland, OH: D. Yurkiw; Denver, CO: E.B. Thumm, J. Buchanan, B. Schmidt, D. Peterson; Hines, IL: P. Linnerud; Indianapolis, IN: K. Moore; Kansas City, MO: J. Gibbs, O. Oni, K. Knepper; Loma Linda, CA: H. Christiansen, S. Read, S. Sumarli, M. Peterson, G. Ding; Long Beach, CA: F. Toussaint-Jones, A. Asghar, T. Reece; Madison, WI: J. Swanlund; Memphis, TN: W.E. Burgess; Miami, FL: L. Albassam, J.E. Johnson, B. Sharpe; Milwaukee, WI: A. Reymann, A. Nyenhuis; Minneapolis, MN: J. Perzynski, J. Tomaska, T. Meyeraan, K.A. Lee; Omaha, NE: K. Malone; Palo Alto, CA: J. Njenga, A. Sarwary, E. Nikolaev, G. Lowe; E.G. Fischer; Philadelphia, PA: S. DiFilippo, T. Rowe; Phoenix, AZ: A. Harms, C. Houser, D.J. Swan, L. Christians, A. Kuramoto, R. Swain, S. Brannan; Pittsburgh, PA: S. Pierce; Salem, VA: T. Yates, S. Cohen; Salisbury, NC: K. Wilson, A. Boaz; San Diego, CA: J. McClure; San Francisco, CA: C. Vasisht, J.G. Crisler; St. Louis, MO: J. Curtin; Tampa, FL: M.A. Fraser; Temple, TX: M. Moore, C. Kuhn; Tucson, AZ: P.R. Duffy, L.E. Price, B.B. Duarte; Tuscaloosa, AL: L. Cheatum; Washington, DC: K.H. Kinaro, E. Nwogu; West Haven, CT: A. Ahmetovic, B. Huguenel, C. Luddy, J.A. Bhat, A. Schnakenberg, P. Purohit;

VA Site Evaluators – Albuquerque, NM: J. Keller, R. Kushner; American Lake/Tacoma, WA: A. Wood, J. MacArthur, K. Dennison; Asheville, NC: C. Fortenberry, K. Barlow; Atlanta, GA: D. Morehead, P. Eilender; Baltimore, MD: A. Corporandy, A. Elliott; Cincinnati, OH: M. Wolfe, D. Suggs; Clarksburg, WV: A. Carpenter, T. Lechliter, R.K. Litton; Cleveland, OH: D. Davis, G. Murmann; Denver, CO: P. Ronan, C. Emrick, C. Dize; Hines, IL: L. Ferguson, B. Dharmaraj; Indianapolis, IN: S. Sidenbender, A.K. Jones, A. Strasburger; Kansas City, MO: A. Papa, A. Le, O. Oni; Loma Linda, CA: A. Hawley, J. Starzyk, L. Krawczyk, V. Simpson; Long Beach, CA: M. Akkinepalli, L.T.X. Nguyen, E. Delvac, M. Dotiu, D. Pineda, K. Isip; Madison, WI: A. Wojtanowski, R. Wilson, V.E. Maine, M. Mualuko, M. Messina; Memphis, TN: L. Gilbert, A. Geno; Miami, FL: M. Suiero; Milwaukee, WI: S. Michalski; R. Faber; Minneapolis, MN: C. Amundson, T. Carr, D. Condon; Omaha, NE: D.M. Driscoll, J. Rose, M.S. Hollibaugh; Palo Alto, CA: B. Raudabaugh, J.H. Nagy, N.S. Feldman, E. Nikolaev, K. Bratcher; Philadelphia, PA: R. Langan, K. Talley; Phoenix, AZ: M. Rukavena, T.P. Franklin, M. Hovis, R. Bohannan; Pittsburgh, PA: K. Daniels; Salem, VA: C. Florow, S. West, D. Arsura; Salisbury, NC: J. Haber, C. Smith, N. Mattila; San Diego, CA: S. Vigeant, K. Seay, Y. Wong, A. Zarkeshfard, C. Fernandes, R. Garcia; San Francisco, CA: J. Huggins, B.M. Jersky, C. Primich; St. Louis, MO: J. O'Leary, L.D. Barnes; Tampa, FL: C. Melillo, P. Palacios; Temple, TX: L.M. Blackburn; Tucson, AZ: M. Beniquez, J. Oehlert, B. Hayes, J. Tsanadis, S. Emert; Tuscaloosa, AL: A. Davis, C.M. Blansett, A. Mahaney-Price, B. Whitfield; Washington, DC: B. Qureshi, N. Rao, D. David; West Haven, CT: K. Forselius-Bielen, M. Carbuto, H. Thurnauer, L. Rispoli, D. DeWorsop.

VA Site Pharmacists – Albuquerque, NM: n/a; American Lake/Tacoma, WA: J. Kim, A. Lokeno; Asheville, NC: G. O'Brien; Atlanta, GA: n/a; Baltimore, MD: H. Jiang; Cincinnati, OH:

E. Costea, B. Fleck; Clarksburg, WV: T. Hedrick; Cleveland, OH: A. Leone, G. Horn, R. Wenzell; Denver, CO: S. Bartlett; Hines, IL: R. Naidu, D. Patel; Indianapolis, IN: W.N. Turner; Kansas City, MO: A. Ungerman, C. Copeland, D. Brown, A. Pastora, K. Adams, J. Miller, A. Sipe, A. Schenk; Loma Linda, CA: W. Lee, R. Yong; Long Beach, CA: P. Shafer, Y. Chi, R. Leong; Madison, WI: A. Schuna; Memphis, TN: T. Edwards; Miami, FL: n/a; Milwaukee, WI: S. Piscatello; Minneapolis, MN: M. Walquist, D. DeCarollis,; Omaha, NE: E. Chandler; Palo Alto, CA: K. Lu, R. Khan; Philadelphia, PA: K. Lynum, L. Middleberg-Warszawski, P.E. Jacobs; Phoenix, AZ: J.P. Nelson; Pittsburgh, PA: S. Podnar, K. Theiroff; Salem, VA: S. Murphy; Salisbury, NC: G. Cazad; San Diego, CA: S. Funk; San Francisco, CA: H. Leung; St. Louis, MO: Andrea Chen; Tampa, FL: T. Eingle; Temple, TX: C. Gough; Tucson, AZ: S. Crawford, D. Hardy; Tuscaloosa, AL: C. Pratt, K. Cameron; Washington, DC: S. Rajendran, R. Hodges; West Haven, CT: S. Perry, R. Galvan.

VA Site Supporting Staff – Albuquerque, NM: G. Fuldauer; American Lake/Tacoma, WA: S. Devroy, L. Maus, P. Jaquish, A. Shen, L. McIntire, C. Wei, N. Moravec, N. Camacho; Asheville, NC: n/a; Atlanta, GA: C. Jasien, S. Jananeh, M. Dvalishvili, O. Mahmoud; Baltimore, MD: J.E. Kindred; Cincinnati, OH: n/a; Clarksburg, WV: G. Nelson, K. Keener; Cleveland, OH: n/a; Denver, CO: F. Miravella, B. Temple; Hines, IL: A. Garabedian, C. McBurney; Indianapolis, IN: n/a; Kansas City, MO: A. Ungerman, C. Copeland, D. Brown, A. Pastora, K. Adams, J. Miller, A. Sipe, A. Schenk; Loma Linda, CA: R.L. Ruybalid, A. Purkeypile, T. Gunneman, J. Kato, A. Sahagian, L. Herold, R. Cordova, T. Copeland, A. Novak, M. Bowie, S. Peresuh, M. Halim, D. Azevedo, R. Carnevale, G. Mamani, J. Salazar, A. Ibarra, A. Gill, Z. Travis; Long Beach, CA: n/a; Madison, WI: n/a; Memphis, TN: S. Lapova; Miami, FL: n/a; Milwaukee, WI: n/a; Minneapolis, MN: A. Klein, E. Latts (deceased); Omaha, NE: K. Shah; Palo Alto, CA: I. Gwizdowski; Philadelphia, PA: R. Hershenberg, E. Harders; Phoenix, AZ: n/a; Pittsburgh, PA: L. Fox, J. Walker; Salem, VA: n/a; Salisbury, NC: n/a; San Diego, CA: J.E. Margolis, D. Beck, M.N. Iqbal, J. Chen, S. Ma, S. Wong, C. Gonzaga, Y. Tu, E. O'Neil; San Francisco, CA: C. Bulsara; St. Louis, MO: H.R. Lustman, K. Semenkovich, K. Waidmann, C.C. Rowe; Tampa, FL: S. Reading, R. Gironda; Temple, TX: S. Justice, K. McNair, C. Valenzuela; Tucson, AZ: n/a; Tuscaloosa, AL: J. Biladeau; Washington, DC: n/a; West Haven, CT: n/a.

Study Co-Chair's Office, VA Connecticut Healthcare System, West Haven, CT – S. Mohamed (Study Co-Chair), H. Carlson; **Study Co-Chair's Office, VA San Diego Healthcare System, San Diego, CA –** S. Zisook (Study Co-Chair), A. Kelada, I. Tal, K. (Weingart) Lauro;

VA Cooperative Studies Program Coordinating Center, VA Connecticut Healthcare System, West Haven, CT – P. Guarino (Director - Past), G.R. Johnson (Acting Director), M. Antonelli, S. Chiu, P. Daniel, K. Dellert, B. Hunter, C. Joncas, D.D. Lawrence, S. O'Neil, B. Planeta, J. Poulton, S. Zellner, K. Kirkwood, M. LeGwin, E.S. Jobes, A. Hatcher;

VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, NM – S.R. Warren (Director), J.E. Vertrees, J. Day, A. Scrymgeour;

VA Cooperative Studies Program Site Monitoring, Auditing and Review Team, Albuquerque, NM – L.A. Calais, J. Dietzler, C. Haakenson, D. Krueger, B.J. McCormick, A. Shontz;

VA Health Economics Resource Center, VA Palo Alto, Menlo Park, CA – J. Yoon, A. Park**;**

VA Office of Research and Development, Clinical Science R&D, Washington, DC – T. O'Leary (Director, CSP; Chief, Research & Development Officer (past)), G.D. Huang (Deputy Director and Acting Director, Cooperative Studies Program);

Appendix 2. Results of mixed effects model of repeated QIDS assessments during the Acute Treatment Phase.

A repeated measures model using general estimating equations (GEE) was defined including

Repeated QIDS total score for Weeks 1 through 12 as the independent response variable

Covariates:

Treatment: AD+ARI, AD+BUP, and Switching to BUP (reference)

PTSD Status (F9HPTSD)" 0 = No PTSD (reference), 1 = PTSD

QIDS_Totalscore_baseline: QIDS-C score at Baseline

Time: Log (Visit_Week) = Log Transform of Visit_Week 1 to 12 (log transform to improve goodness of fit of repeated measures model)

Interaction terms for Treatment x PTSD status

Interaction terms for Treatment x Log (Visit_Week) – to assess any treatment interaction over time.

MODEL:

$QIDS_{ij}=\beta_0 + \beta_1*I_{(AD+ARI)} +\beta_2*I_{(AD+BUP)} + \beta_3*I_{(PTSD)} + \beta_4*I_{(AD+ARI)}*I_{PTSD} +$

$\beta_5* I_{(AD+BUP)} * I_{PTSD} + \beta_6*\text{Log (Visit week)} + \beta_7*\text{Log (Visit week)}* I_{(AD+ARI)} + \beta_8*\text{Log (Visit week)}* I_{(AD+BUP)} +$

β_9*QIDS-C_baseline

where **I** is the indicator variable for treatment group or PTSD status and $QIDS_{ij}$ is the QIDS score of individual i at week j.

Supplementary Table 1: Table showing the results of the repeated measures model

Variable	Effect	Estimate	95% Confidence Limits	p-value
Intercept		3.2329	(2.098, 4.368)	<.0001
Treatment	AD+ARI vs Switch to BUP	-0.5504	(-1.262, 0.161)	0.13
	AD+BUP vs Switch to BUP	0.0636	(-0.639, 0.767)	0.86
PTSD status	No vs Yes	-0.910	(-1.583, -0.236)	0.008
Treatment*PTSD	AD+ARI No vs Yes	0.029	(-0.914, 0.971)	0.95
	AD+BUP No vs Yes	-0.1707	(-1.111, 0.769)	0.72
log(week)		-1.579	(-1.775, -1.383)	<.0001
log(week)*treatment	AD+ARI vs Switch to BUP	-0.122	(-0.389, 0.145)	0.37
	AD+BUP vs Switch to BUP	-0.161	(-0.426, 0.104)	0.23
Baseline QIDS score		0.601	(0.541, 0.661)	<.0001

Supplementary Table 2. Withdrawal Before Week 12 and Reason for Withdrawal by Treatment Group and PTSD Status

Withdrawal Before Week 12 and Reason for Withdrawal	Switch-BUP					Augment-BUP					Augment-ARI				
	No PTSD		PTSD		All	No PTSD		PTSD		All	No PTSD		PTSD		All
	N	%	N	%		N	%	N	%		N	%	N	%	
Withdrawn before Week 12	79	30.0	79	31.9	158	56	21.4	72	29.5	128	52	18.6	47	20.9	99
Side Effects	*24*	*9.1*	*29*	*11.7*	*53*	*27*	*10.3*	*11*	*4.5*	*38*	*18*	*6.4*	*9*	*4.0*	*27*
Lack of Treatment Effect	*28*	*10.6*	*21*	*8.5*	*49*	*10*	*3.8*	*18*	*7.4*	*28*	*6*	*2.1*	*7*	*3.1*	*13*
Other	*27*	*10.3*	*29*	*11.7*	*56*	*19*	*7.3*	*43*	*17.6*	*62*	*28*	*10.0*	*31*	*13.8*	*59*
Completed Week 12	184	70.0	169	68.1	353	206	78.6	172	70.5	378	228	81.4	178	79.1	101
Total	263	100.0	248	100.0	511	262	100.0	244	100.0	506	280	100.0	225	100.0	505

Supplementary Table 3: Table showing the difference between least square means of QIDS scores by treatment category and PTSD status.

Treatment Comparison	PTSD	Estimate	Pr > |z|
AD+ARI vs Switch to BUP	no	-0.700	0.026
AD+ARI vs Switch to BUP	yes	-0.728	0.045
AD+ARI vs AD+BUP	no	-0.357	0.251
AD+ARI vs AD+BUP	yes	-0.557	0.130
AD+BUP vs Switch to BUP	no	-0.342	0.284
AD+BUP vs Switch to BUP	yes	-0.172	0.632