EDITORIAL

Lessons Learned From the VA Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) Study

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In this issue of *JAMA*, Mohamed and colleagues[1] report the outcome of an important multicenter clinical trial, the Veterans Affairs Augmentation and Switching Treatments for Improving Depression Outcomes (VAST-D) Study. The study, conducted with scientific rigor and sophisticated clinical trial methodology, compared the relative effectiveness and safety of 3 commonly used treatment options for 1522 patients with major depressive disorder (MDD) with inadequate response to antidepressant therapy: switching to a different antidepressant, which was bupropion in this study (n = 511); augmenting current treatment with bupropion (n = 506); or augmenting current treatment with an atypical antipsychotic drug, which was aripiprazole in this study (n = 505). The primary outcome was remission of depression (defined as a 16-item Quick Inventory of Depressive Symptomatology-Clinician Rated [QIDS-C_{16}] questionnaire score of ≤5 at 2 consecutive visits) after 12 weeks of acute treatment. Additional outcomes included response (≥50% reduction in QIDS-C_{16} score or improvement on the Clinical Global Impression [CGI] Global Improvement scale), as well as relapse, and adverse effects. Patients who achieved remission at 12 weeks (n = 396) were followed for relapse for up to 36 weeks after randomization.

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The study was adequately powered to detect small effect sizes and showed a modest yet significant advantage for augmenting treatment with aripiprazole compared with switching to bupropion (in terms of both higher remission and response rates) and augmenting treatment with bupropion (in terms of higher response rates only). Remission rates were 22% for patients who switched to bupropion, 27% for those who augmented treatment with bupropion, and 29% for those who augmented treatment with aripiprazole. Response was greater for those who augmented treatment with aripiprazole (74%) than those either switching to bupropion alone (62%) or augmenting treatment with bupropion (66%). No significant treatment differences were observed in terms of relapse rates among patients who experienced remission. Anxiety was most frequent in the 2 bupropion groups, whereas somnolence, akathisia, and weight gain were most common among patients treated with aripiprazole.

The VAST-D study provides an important comparison of the effectiveness and tolerability of atypical antipsychotic augmentation with findings from 2 of the relatively effective treatment options in level 2 of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial,[2] whereby patients with MDD who had not responded adequately to an initial prospective trial with the antidepressant citalopram were randomized to 1 of 7 treatment options. In the STAR*D study, originally designed at a time when no atypical antipsychotic drug had been approved yet for antidepressant augmentation by the US Food and Drug Administration (FDA), the option of atypical antipsychotic augmentation was not included in any of the treatment options studied.

Since the completion of the STAR*D study, augmentation with atypical antipsychotic drugs, for which the efficacy is now well established,[3] has become 1 of the most common pharmacological approaches for patients with resistant depression, with 3 of these drugs (aripiprazole, quetiapine, brexpiprazole) having FDA approval for this indication, or with the fixed combination of fluoxetine and olanzapine. However, a recent survey of 154 US psychopharmacologists[4] indicated that atypical antipsychotic augmentation was only a fourth-line consideration, suggesting some reluctance to use this approach earlier in the algorithm used by clinicians for treatment of resistant depression. The modest advantage of aripiprazole augmentation over the 2 other treatment options in the VAST-D study suggests that this approach should be considered earlier by clinicians for patients with MDD who have an inadequate response to antidepressant therapies.

Because the VAST-D study was implemented solely in VA sites, the population studied was predominantly male (85%), a significant difference from the usual study population in large trials of MDD, in which women typically far exceed the proportion of male study participants, as was the case with STAR*D.[2] Accordingly, the study cannot determine whether the results would have been different in a predominantly female population of patients with MDD. However, a pooled analysis of 2 trials comparing aripiprazole augmentation with placebo augmentation among patients with MDD and inadequate response to antidepressant therapy found that aripiprazole augmentation was actually more effective for women than men.[5] This argues that the VAST-D study may have underestimated the relative benefit of aripiprazole augmentation.

The mean number of previously unresponsive courses of antidepressant therapy among patients enrolled in the VAST-D study ranged from 2.3 to 2.5, suggesting that the enrolled population was similar to the one included in level 3 of the STAR*D study, in which patients were randomized to 1 of 4 treatment options after having no treatment response to 2 prospective trials of antidepressant treatment

through levels 1 and 2. Among the STAR*D patients in level 3, the remission rates ranged between 15.9% with lithium augmentation and 24.7% with T_3 augmentation[6] and between 12.3% with a switch to mirtazapine and 19.8% with a switch to nortriptyline.[7] The remission rates reported in the VAST-D study, 22% for the switch to bupropion, 27% for bupropion augmentation, and 29% for aripiprazole augmentation, are consistent with those observed among patients in level 3 of STAR*D, albeit somewhat higher. It is possible that the retrospective assessment of antidepressant therapy resistance in the VAST-D study compared with the prospective determination of resistance in the STAR*D study may account for these small differences.

Another significant difference between the VAST-D and STAR*D studies is that between 44% and 48% of patients in the VAST-D study had posttraumatic stress disorder (PTSD), whereas the rate of PTSD at baseline in STAR*D was only 17%.[8] Did such enrichment potentially favor one of the treatment options of VAST-D? Although a placebo-controlled study of bupropion in chronic PTSD showed no benefit of this therapy,[9] a meta-analysis of 8 randomized, double-blind, placebo-controlled clinical trials of atypical antipsychotics for the treatment of PTSD found that these agents may be superior to placebo in the treatment of PTSD, as indicated by the changes in Clinician Administered PTSD Scale (CAPS) total scores (weighted mean difference [WMD], −5.89 [95% CI, −9.21 to −2.56], P< .001) and also in CAPS subscale intrusion (WMD, −2.58 [95% CI, −3.83 to −1.33], P < .001) and subscale hyperarousal (WMD, −2.94 [95% CI, −5.45 to −0.43], P = .02).[10] In addition, a cross-sectional European multicenter study found that comorbid PTSD among patients with MDD was associated with higher rates of use of augmentation with low-dose antipsychotics (odds ratio, 6.66 [95% CI, 2.50 to 17.77]; P < .001).[11] This suggests that clinicians recognize the therapeutic benefit of adding drugs such as aripiprazole in the treatment of MDD complicated by PTSD and supports the view that the modest advantage of aripiprazole augmentation in the VAST-D study may be partly due to the enrichment in patients with MDD and comorbid PTSD.

In addition, the mean age of onset of MDD among patients in the VAST-D study ranged between 36 and 38 years, in contrast to the younger mean age of onset of 25 years in the STAR*D study.[8] The older age of onset of MDD in the VAST-D study suggests that in many cases the MDD may have been secondary to other psychiatric conditions, such as PTSD. Therefore, there might be some significant neurobiological differences between the 2 populations.

Another interesting methodological aspect of the VAST-D study was the asymmetry between the minimal requirement of duration of the failed antidepressant therapy prior to randomization (6 or 8 weeks) and the duration of acute treatment during the randomized trial (12 weeks). Some methodological purists would argue that 6 or 8 weeks of antidepressant treatment is an inadequate period to declare inadequate response because many patients may respond only after 8 to 14 weeks of treatment.[2] On the other hand, the approach used in the study is ecologically valid, as in practice clinicians are unlikely to wait 3 months before taking the next therapeutic step for patients who have an inadequate response to antidepressant therapy.

The marked differences in tolerability across the 3 treatment options of the VAST-D study are consistent with the published literature on these medications. Anxiety was the most frequent adverse effect in the 2 bupropion groups, whereas somnolence, akathisia, and weight gain were most common adverse events among patients treated with aripiprazole. The adverse effect profile of these treatments can help clinicians determine what the best next-step treatment should be for a given patient with MDD and inadequate response to antidepressant therapy.

In summary, the findings of the VAST-D study reported by Mohamed and colleagues in this issue of *JAMA* showed a modest yet significant advantage for the aripiprazole augmentation compared with switching to bupropion (in terms of both higher remission and response rates) and bupropion augmentation (in terms of higher response rates only) in a population of patients with MDD and inadequate response to antidepressant therapy. The VAST-D study was uniquely enriched by men and by those with PTSD comorbidity, and offers an important perspective on the role of treatment using augmentation with atypical antipsychotic agents in this population commonly seen in VA clinics.

ARTICLE INFORMATION

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Does Obstructive Sleep Apnea Treatment Reduce Cardiovascular Risk?

It Is Far Too Soon to Say

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The association of obstructive sleep apnea (OSA) with vascular disease and mortality was reported in clinical case series almost 3 decades ago and has since been confirmed in numerous prospective observational studies involving both sleep clinic patients and community-based cohorts. Physiological studies in animals and humans have suggested likely mechanisms whereby the intermittent hypercapnic hypoxemia and recurrent arousal from sleep that characterize OSA might cause vascular disease. The most strongly implicated mechanism is increased sympathetic nervous system activity, with considerable evidence as well for impaired glucose homeostasis, vascular inflammation, and oxidative stress.[1] Numerous single-site and multicenter studies have demonstrated modest but clinically significant reductions in blood pressure with OSA treatment, an effect that is substantial during sleep.[2-4] This effect alone would be expected to result in a reduction in risk of myocardial infarction and stroke. Clinical cohort studies comparing patients with OSA treated with positive airway pressure (PAP) with untreated patients with OSA have consistently demonstrated lower rates of death, myocardial infarction, and stroke among the treated patients.[5] However, such observational studies carry a substantial risk of bias due to a "healthy adherer" effect, and randomized clinical trials (RCTs) are therefore necessary to demonstrate whether treatment of OSA does reduce cardiovascular risk.

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In this issue of *JAMA*, Yu and colleagues[6] present the results of a meta-analysis of RCTs evaluating the relationship of PAP treatment for sleep apnea with major adverse cardiovascular events (including a composite of acute coronary syndrome events, stroke, or vascular death) and mortality. Based on analyses of data from 10 trials of patients with sleep apnea (N = 7266; 5683 with OSA, 1583 with central sleep apnea; 80.5% men; mean body mass index 30.0), and 356 major adverse cardiovascular events and 613 deaths, the authors found no significant association between PAP and major adverse cardiovascular events (relative risk [RR], 0.77 [95% CI, 0.53 to 1.13]; P = .19 and risk difference [RD], −0.01 [95% CI, −0.03 to 0.01]; P = .23), cardiovascular death (RR, 1.15 [95% CI, 0.88 to 1.50]; P = .30 and RD, −0.00 [95% CI, −0.02 to 0.02]; P = .87) or all-cause death (RR, 1.13 [95% CI, 0.99 to 1.29]; P = .08 and RD, 0.00 [95% CI, −0.01 to 0.01]; P = .51). The authors note that the evidence from these RCTs "suggests that the association of sleep apnea with vascular outcomes and death seen in observational studies may represent disease processes that cannot be ameliorated by PAP delivered at the average intensity achieved in these clinical trials or currently feasible in clinical practice."

Although the authors identified and evaluated the available evidence regarding PAP for sleep apnea, their conclusion appears premature. Indeed, perhaps the most important finding of this meta-analysis is the paucity of informative clinical trial data. The primary focus of the meta-analysis was a composite outcome of acute coronary events, stroke, or cardiovascular death among patients with OSA. The separate meta-analysis of mortality is of uncertain validity, as it includes studies of central sleep apnea in patients with heart failure, a condition with considerably different pathophysiology from OSA. Only 7 studies were identified that met inclusion criteria for the analysis of PAP in patients with OSA, and these were a heterogeneous group that included primary and secondary prevention studies with mean follow-up durations of 6 months to 6 years and mean PAP adherence of 1.4 to 6.6 hours per night. These studies included a total of only 4562 patients and 356 outcome events, of which 73% were contributed by a single study (ie, the Sleep Apnea Cardiovascular Endpoints (SAVE) study[7]).

In the meta-analysis by Yu et al,[6] the estimated relative risk for the association between CPAP and the composite outcome of acute coronary events, stroke, or cardiovascular death was 0.77 (95% CI, 0.53 to 1.13), which is similar to the estimated risk reduction associated with antiplatelet therapy,[8] statins,[9] and β-adrenergic blockers[10] in reducing recurrent vascular events. Although this point estimate was not statistically significant, if this relative risk reduction were real, it would be of substantial clinical importance.