Adjunctive Risperidone Treatment for Antidepressant-Resistant Symptoms of Chronic Military Service–Related PTSD

A Randomized Trial

John H. Krystal, MD
Robert A. Rosenheck, MD
Joyce A. Cramer, BS
Jennifer C. Vessicchio, MSW
Karen M. Jones, MS
Julia E. Vertrees, PharmD
Rebecca A. Horney, BA
Grant D. Huang, MPH, PhD
Christopher Stock, PharmD
for the Veterans Affairs Cooperative Study No. 504 Group

Context Serotonin reuptake-inhibiting (SRI) antidepressants are the only FDA-approved pharmacotherapies for the treatment of posttraumatic stress disorder (PTSD).

Objective To determine efficacy of the second-generation antipsychotic risperidone as an adjunct to ongoing pharmacologic and psychosocial treatments for veterans with chronic military-related PTSD.

Design, Setting, and Participants A 6-month, randomized, double-blind, placebo-controlled multicenter trial conducted between February 2007 and February 2010 at 23 Veterans Administration outpatient medical centers. Of the 367 patients screened, 296 were diagnosed with military-related PTSD and had ongoing symptoms despite at least 2 adequate SRI treatments, and 247 contributed to analysis of the primary outcome measure.

Intervention Risperidone (up to 4 mg once daily) or placebo.

Main Outcome Measures The Clinician-Administered PTSD Scale (CAPS) (range, 0-136). Other measures included the Montgomery-Asberg Depression Rating Scale (MADRS), Hamilton Anxiety Scale (HAMA), Clinical Global Impression scale (CGI), and Veterans RAND 36-Item Health Survey (SF-36V).

Results Change in CAPS scores from baseline to 24 weeks in the risperidone group was –16.3 (95% CI, –19.7 to –12.9) and in the placebo group, –12.5 (95% CI, –15.7 to –9.4); the mean difference was 3.74 (95% CI, –0.86 to 8.35; $t=1.6$; $P=.11$). Mixed model analysis of all time points also showed no significant difference in CAPS score (risperidone: mean, 64.43; 95% CI, 61.98 to 66.89, vs placebo: mean, 67.16; 95% CI, 64.71 to 69.62; mean difference, 2.73; 95% CI, –0.74 to 6.20; $P=.12$). Risperidone did not reduce symptoms of depression (MADRS mean difference, 1.19; 95% CI, –0.29 to 2.68; $P=.11$) or anxiety (HAMA mean difference, 1.16; 95% CI, –0.18 to 2.51; $P=.09$; patient-rated CGI mean difference, 0.20; 95% CI, –0.06 to 0.45; $P=.14$; observer-rated CGI mean difference, 0.18; 95% CI, 0.01 to 0.34; $P=.04$), or increase quality of life (SF-36V physical component mean difference, –1.13, 95% CI, –2.58 to 0.32; $P=.13$; SF-36V mental component mean difference, –0.26; 95% CI, –2.13 to 1.61; $P=.79$). Adverse events were more common with risperidone vs placebo, including self-reported weight gain (15.3% vs 2.3%), fatigue (13.7% vs 0.0%), somnolence (9.9% vs 1.5%), and hypersalivation (9.9% vs 0.8%), respectively.

Conclusion Among patients with military-related PTSD with SRI-resistant symptoms, 6-month treatment with risperidone compared with placebo did not reduce PTSD symptoms.

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POSTTRAUMATIC STRESS DISORDER (PTSD) is among the most common and disabling psychiatric disorders among military personnel serving in combat theaters.[1-3] Antidepressants are the predominant pharmacotherapy for PTSD. Two serotonin reuptake inhibitors (SRIs), sertraline and paroxetine, have Food and Drug Administration approval for the treatment of PTSD based on multicenter trials.[4-7] Within the Department of Veterans Affairs (VA), 89% of veterans diagnosed with PTSD and treated with pharmacotherapy are prescribed SRIs.[8] However, SRIs appear to be less effective in men than in women[4] and less effective in chronic PTSD than in acute PTSD.[9,10] Thus, it may not be surprising that an SRI study in veterans produced negative results.[11]

For editorial comment see p 549.

Second-generation antipsychotics (SGAs) are commonly used medications for SRI-resistant PTSD symptoms, despite limited evidence support-

Author Affiliations and Members of the Veterans Affairs Cooperative Study No. 504 Group are listed at the end of this article.
Corresponding Author: John H. Krystal, MD, VA Connecticut Healthcare System (151-D), 950 Campbell Ave, West Haven, CT 06516 (john.krystal@yale.edu).

ing this practice.[12,13] In 2007, PTSD was the most common off-label diagnosis within the VA associated with an antipsychotic prescription.[14] In 2009, 86 852 veterans diagnosed with PTSD (19.9%) received an antipsychotic prescription and 81 279 of these prescriptions (93.6%) were for SGAs.[14] There are substantial safety concerns associated with SGAs, particularly risks for weight gain and extrapyramidal motor symptoms.[15]

The current study evaluated whether risperidone, an SGA, when added to an ongoing pharmacotherapy regimen would be more effective than placebo for reducing chronic military-related PTSD symptoms among veterans whose symptoms did not respond to at least 2 adequate SRI treatments. To our knowledge, this study is the first large trial of a pharmacotherapy aimed at SRI-resistant PTSD symptoms.

METHODS

Patients were eligible if they were at least 18 years old, participated in a military combat theater, met diagnostic criteria for military service–related chronic PTSD on the basis of a structured interview for making psychiatric diagnoses according to the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition) (*DSM-IV*),[16] had a Clinician-Administered PTSD Scale (CAPS) score greater than 50,[17] had a clinical history of intolerance of or nonresponse to 2 or more antidepressants, and had an inadequate response to 2 adequate SRI treatments (minimum of 4 weeks of pharmacotherapy each). Other eligibility criteria included having a fixed address within 50 miles of the research site or confirmed transportation for all visits, using an acceptable method of birth control (female patients), and giving written informed consent.

Patients were excluded if they met lifetime diagnostic criteria for bipolar disorder or schizophrenia; required antipsychotic medication for the treatment of psychosis; met diagnostic criteria for dependence on a substance other than nicotine in the 30 days prior to screening; had clinical or laboratory evidence (levels of aspartate aminotransferase, alanine aminotransferase, bilirubin, blood urea nitrogen, or creatinine) of hepatic or renal compromise; had a medical disorder that might increase the risks of risperidone treatment (insulin-dependent diabetes) or complicate interpretation of study results (epilepsy, dementia); had a history of intolerance of antipsychotics; attempted suicide or assaulted someone in the prior year; or had an impending legal incarceration. Although ongoing pharmacotherapy was allowed, patients receiving SGAs, serotonergic ($5HT_2$) receptor antagonists (cyproheptadine, methysergide, trazodone), α_1 receptor antagonists (prazosin), and α_2 receptor agonists/antagonists (clonidine, guanfacine, mirtazapine) were excluded initially.

Race and ethnicity of the participants were determined by self-reports with concurrence by the rater.

Interventions

The human subjects subcommittees of the VA Cooperative Studies Program and each participating VA Medical Center approved this study. All patients gave written informed consent prior to study entry. An independent data safety monitoring board monitored patient safety throughout the study.

Patients were randomized to receive double-blinded 6-month treatment with risperidone or matched placebo. Study medication (risperidone 1 mg or matching placebo) was initiated at a dose of 1 tablet orally at bedtime and increased by 1 tablet per week to a dose of 3 tablets at bedtime. After participants received study medication for 4 weeks, investigators who were blinded to study medication status and were treating patients had the option of further increasing the dose by 1 tablet (1 mg), providing medications were well tolerated and a dose increase was indicated clinically.

Prior to study entry, patients and their primary mental health care clinicians developed a treatment plan that would not violate study protocol and would be engaged if study medications were ineffective. These alternative treatments enabled some patients to remain as participants for the full 6 months of randomized treatment (eTable 1, available at http://www.jama.com). There were no significant differences across groups in the frequency with which these adjunctive medications from particular classes were initiated during the clinical trial.

Patients participated in a feedback program that was designed to enhance adherence to prescribed medications.[18,19] Medication was provided in bottles with microelectronic monitor caps (MEMS; AARDEX Group, Union City, California) that recorded the date and time of each opening and showed the number of hours elapsed since the previous opening. The Medication Usage Skills for Effectiveness feedback system,[18] in which data on the previous month's dosing were shown to patients at each visit, encouraged patients to take medication daily by training them to develop and use reminders that supported medication adherence.

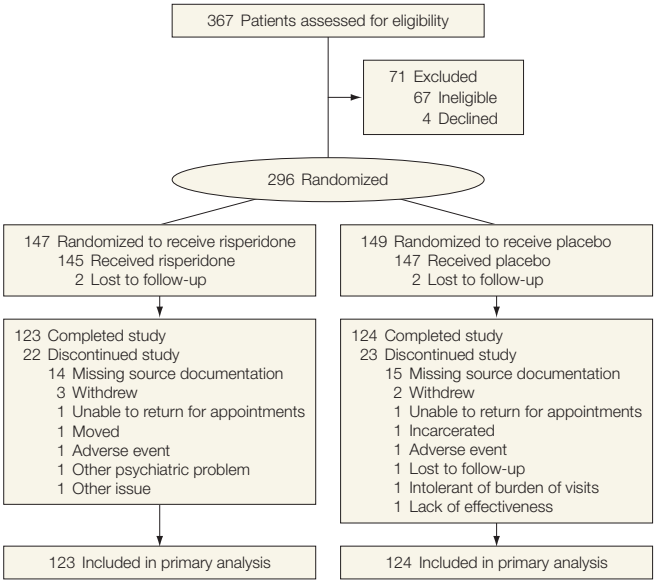
Randomization and Treatment

Patients were recruited initially from 20 VA Medical Centers over a 2-year period. To address low recruitment rates and other issues, 8 sites were discontinued and 6 sites were added during the course of the study. A total of 26 sites were approved by the human subjects subcommittee to enroll patients into the study. In addition, the recruitment period was extended by 6 months, and patients who had initially been considered ineligible to participate in the study because they were receiving certain drugs (trazodone ≤100 mg, nefazodone ≤100 mg, quetiapine ≤25 mg, and mirtazapine ≤30 mg) were allowed if the drugs were prescribed for at least 3 months prior to screening and prescribed at the current dose for at least 1 month. A total of 83 patients (42 in the risperidone group, 41 in the placebo group) who were ultimately enrolled in this study had received at least 1 of these medications. Secondary analyses testing the effect of broaden-

ing the study entry criteria did not find any effects on the findings for the principal outcome measures.

Randomized assignment of patients to treatment groups was conducted by the Cooperative Studies Program Coordinating Center (Perry Point, Maryland). Calls requesting randomization went to a central location on the day the patient was deemed eligible and ready to start medication. Separate randomization schedules were generated for each participating center, assigning equal numbers of patients to each of the groups. Block sizes of 2 and 4 were used to balance assignments across groups and to prevent decoding of the system. Assignments were stratified within centers. Patients were evaluated to ensure they met all eligibility criteria before a randomization code was provided. Treatment was initiated within a day of randomization.

Figure 1. Recruitment Flowchart in Clinical Trial of Risperidone Treatment for Military Service–Related Posttraumatic Stress Disorder



Valid baseline data were collected for 267 patients; the primary outcome analysis included 247 patients for whom a valid week-24 CAPS assessment was obtained.

Outcome Measures

The primary outcome measure for this study was the total score on the 34-item CAPS.[20] This scale was administered by trained raters who were blind to the randomization status of patients at baseline and weeks 6, 12, and 24. All raters underwent initial training and credentialing to administer and score the primary and secondary outcome measures. They also completed annual training and reliability checks during the study to ensure that they met at least 80% reliability of their measurement; all raters eventually met this reliability standard. Interrater reliability was assessed at 2 annual subsequent time points. All raters showed 100% diagnostic accuracy at both sessions, and median scores were within 0.5 points and 3 points at the 2 annual follow-ups, respectively.

The CAPS provided an overall measure of PTSD symptom severity. Secondary outcomes were assessed each time the CAPS was administered: the observer-rated and patient-rated Clinical Global Impression scale (CGI), the Montgomery-Asberg Depression Rating Scale (MADRS),[21] the Hamilton Anxiety Scale (HAMA),[22] a scale used to rate psychosis (Positive and Negative Syndrome Scale [PANSS]),[23] the Veterans RAND 36-Item Health Survey (SF-36V),[24] the 26-item Boston Life Satisfaction Inventory (BLSI),[25] and a service utilization measure. At each visit, smoking was assessed using the first 3 items of the Fagerström Scale,[26] and alcohol consumption was evaluated using the timeline follow-back method for the 90 days prior to study entry and the interval between each visit.[27] Motor adverse events associated with risperidone were assessed using the Barnes Akathisia Scale,[28] the Extrapyramidal Symptom Rating Scale,[29] and the Abnormal Involuntary Movement Scale.[30] On all reported outcome measures except the SF-36V, higher scores reflect higher symptom levels. On the SF-36V, higher scores reflect higher quality of life.

Data Analyses

Data were collected and analyzed by the VA Cooperative Studies Program. Baseline characteristics were compared with χ^2 and t tests as appropriate.

The primary outcome measure in this study was the intent-to-treat analysis of the improvement in PTSD symptoms from baseline to week-24 follow-up as measured by the CAPS. A 2-tailed t test was performed on these data using an $\alpha = .05$. This study was powered initially to detect a 9-point difference between the treatment groups in the CAPS change score; assuming a 20% dropout rate and a power of 0.9, a target sample size of 205 patients per group was required. In the absence of a validated threshold for minimal important difference on the CAPS, the threshold of 9 points was derived from data suggesting the following: (1) a 9-point decrease would be predicted to produce clearly evident changes in core PTSD symptoms[31,32]; (2) 9 points was estimated to be approximately 0.5 SD in severely symptomatic veterans with PTSD,[33] and across medical conditions score reductions of 0.5 SD are generally found to be a minimal important difference[34]; and (3) 9- to 10-point decreases would be expected to be associated with improvements in measures of quality of life.[35]

The recruitment rate was lower than projected, with a total of 296 randomized patients rather than the targeted 410.

However, both the dropout rate and the variance in the data were lower than projected, offsetting the effects of the actual sample size on the statistical power of the study. Two hundred forty-seven patients (123 per group, for purposes of power calculation) completed the study. Based on the original parameters for study sample size, an $\alpha = .05$, and the estimated pooled 18.4 SD, this sample size provided 96.9% power to detect a 9-point difference between the groups in the primary outcome measure—ie, the difference between baseline and week-24 CAPS scores.

In secondary and exploratory analyses, the CAPS, its subscales, and all other continuous outcome measures were analyzed using mixed models,[36] covarying for baseline values and using all available outcome data. The models initially had fixed effects for treatment group and time. The interactions between treatment and time effects were dropped because they were not significant in reported analyses. Site and patient were treated as random effects. Generalized least squares means of treatment effect were computed within the SAS mixed linear models procedures (MIXED and GLIMMIX) used to analyze outcome data (SAS Institute, Cary, North Carolina). These least squares means are estimators of the treatment means that would be expected for a balanced design.

In post hoc analyses, the severity of the 3 component clusters of PTSD symptoms associated with *DSM-IV-TR* diagnostic criteria[37]—reexperiencing, avoidance/numbing, and hyperarousal[20]—were analyzed separately with Bonferroni adjustments for multiple comparisons. Also, treatment effects on PTSD severity categories based on the CAPS[32] were analyzed using a 2-tailed χ^2 test. This analysis yielded an estimate of medication effects on remission rates in this study as defined by a CAPS score of less than 20.[38]

A comparison of the treatment groups on retention in the study was based on survival analysis of time (days) receiving study medication as measured from the day of randomization to the day of last dose. Survival curves for study retention were estimated for each treatment group with Kaplan-Meier methodology (SAS procedure LIFETEST), and treatment group comparisons were based on the log-rank test.

Table 1. Baseline Demographic Data

	Risperidone (n = 133)	Placebo (n = 134)	Total (N = 267)	*P* Value
Age, mean (SD), y	54.2 (10.8)	54.5 (10.6)	54.4 (10.7)	.82[a]
Sex, No. (%)				
Male	128 (96.2)	130 (97.0)	258 (96.6)	.75[b]
Female	5 (3.8)	4 (3.0)	9 (3.4)	
Race/ethnicity, No. (%)				
White, not Hispanic	84 (63.2)	93 (69.4)	177 (66.3)	.57[b]
Black, not Hispanic	25 (18.8)	25 (18.7)	50 (18.7)	
Hispanic	16 (12.0)	11 (8.2)	27 (10.1)	
Other	8 (6.0)	5 (3.7)	13 (4.9)	
Weight, mean (SD), lb[c]	205.3 (38.8)	214.0 (46.1)	209.6 (42.7)	.11[a]
Marital status, No. (%)[d]				
Single	20 (15.0)	19 (14.2)	39 (14.6)	.29[b]
Married	67 (50.4)	73 (54.5)	140 (52.4)	
Widowed	0	2 (1.5)	2 (0.7)	
Divorced	36 (27.1)	24 (17.9)	60 (22.5)	
Separated	5 (3.8)	10 (7.5)	15 (5.6)	
Living with partner	5 (3.8)	5 (3.7)	10 (3.7)	
Education, mean (SD), y[e]	14.2 (2.7)	14.1 (2.2)	14.1 (2.5)	.82[a]
Employment (current), No. (%)[d]				
Full time	49 (36.8)	48 (35.8)	97 (36.3)	.94[b]
Part time	6 (4.5)	4 (3.0)	10 (3.7)	
Irregular, part time	7 (5.3)	7 (5.2)	14 (5.2)	
Unemployed	17 (12.8)	21 (15.7)	38 (14.2)	
Other	54 (40.6)	53 (39.6)	107 (40.1)	
Military history, No. (%)				
WWI, WWII, Korea, Vietnam	95 (71.4)	98 (73.1)	193 (72.3)	.67[b]
Gulf War, Afghanistan, Iraq	34 (25.6)	29 (21.6)	63 (23.6)	
Balkans, other war	1 (0.8)	3 (2.2)	4 (1.5)	
Peace time	3 (2.3)	4 (3.0)	7 (2.6)	

Abbreviations: WWI, World War I; WWII, World War II.
[a] *t* Test.
[b] Fisher exact test.
[c] Data were missing for 13 patients.
[d] Data were missing or incorrect for 1 patient in the placebo group (0.4% of total patients).
[e] Data were missing for 2 patients.

RESULTS

Of the 26 sites that were approved to enroll patients into the study, 23 sites enrolled patients from February 2007 to August 2009, with follow-up ending in February 2010. A total of 367 patients screened yielded 296 patients diagnosed with military-related PTSD with clinically significant SRI-resistant PTSD symptoms who signed consent forms from 23 sites (FIGURE 1). Valid diagnostic and primary outcome data were collected on 267 patients randomized to receive risperidone (n = 133) and placebo (n = 134) treatment.

The study populations included severely ill patients, many of whom had disabilities related to long-standing military-related PTSD (TABLE 1, TABLE 2, and TABLE 3). The sample was predominately male (n = 258, 96.6%), middle-aged (mean [SD] age, 54.4 [10.7] years), non-Hispanic white (n = 177, 66.3%), and married (n = 140, 52.4%) or divorced (n = 60, 22.5%). Most patients served during the Vietnam war or earlier (n = 193, 72.3%) or the wars in Iraq and Afghanistan (n = 63, 23.6%). Their PTSD symptoms were attributed principally to direct participa-

tion in combat (n=209, 78.3%). The majority of patients in this study also met lifetime diagnostic criteria for major depression (n=186, 69.7%) and lifetime alcohol abuse or dependence (n=167, 62.5%). Smaller numbers of patients were smokers (n=88, 33.0%) or met diagnostic criteria for other lifetime substance abuse or dependence, antisocial personality disorder, or other mood/anxiety disorders.

Most patients in this study received VA service–connected disability compensation (n=223, 83.5%), of which 181 (81.2%) and 163 (73.1%) had psychiatric and medical disability, respectively. More than one-third of patients (n=99, 37.1%) received a Social Security pension. Patients in this study received typical psychosocial treatments at the medical centers. Based on data collected with a service utilization measure, patients had received the following VA services in the month preceding study entry: 195 patients (74.1%) had received outpatient mental health treatment; 43 patients (16.4%), case management; 16 (6.1%), readjustment counseling; and 15 (5.7%), addiction services. Less than 5% of the sample received any other specified service. There were no significant differences between the groups in service utilization.

The patients in this study were highly symptomatic at study baseline despite long-standing individualized pharmacologic treatments (mean [SD] medications per patient: risperidone, 3.09 [1.69]; placebo, 2.86 [1.46]) (eTable 2 and eTable 3). There were no significant differences in the frequency with which medications other than SRIs were prescribed across the groups prior to randomization or in various combinations of medications (eTable 4). Mean (SD) CAPS total score at study entry was 78.2 (14.8), associated with high levels of reexperiencing (20.9 [6.4]), avoidance/numbing (31.5 [8.1]), and hyperarousal (25.9 [4.9]) symptoms. Patients were significantly depressed (mean [SD] MADRS score, 23.4 [8.2]) and anxious (mean [SD] HAMA score, 19.4 [7.8]), with low levels of psychotic symptoms (mean [SD] PANSS positive symptom score, 11.6 [3.9]).

Table 2. Disability and Service Utilization at Baseline[a]

	Risperidone (n = 133)	Placebo (n = 134)	Total (N = 267)	*P* Value
VA disability pension, No. (%)				
Yes	112 (84.2)	111 (82.8)	223 (83.5)	.87[b]
No	21 (15.8)	23 (17.2)	44 (16.5)	
Medical disability, No. (%)				
Yes	83 (74.1)	80 (72.1)	163 (73.1)	.76[b]
No	29 (25.9)	31 (27.9)	60 (26.9)	
Medical disability, mean (SD), %[d]	34.5 (31.8)	31.8 (23.5)	33.2 (28.0)	.55[c]
Psychiatric disability, No. (%)				
Yes	89 (79.5)	92 (82.9)	181 (81.2)	.61[b]
No	23 (20.5)	19 (17.1)	42 (18.8)	
Psychiatric disability , mean (SD), %[e]	63.4 (28.1)	65.3 (25.2)	64.4 (26.6)	.62[c]
Social Security pension, No. (%)				
Yes	50 (37.6)	49 (36.6)	99 (37.1)	.90[b]
No	83 (62.4)	85 (63.4)	168 (62.9)	
VA service use, No. (%)				
Outpatient mental health	102 (77.9)	93 (70.5)	195 (74.1)	.40[b]
Case management	21 (16.0)	22 (16.7)	43 (16.4)	.81[b]
Alcohol/drug abuse clinic	8 (6.1)	7 (5.3)	15 (5.7)	.74[b]
Rehabilitation program	6 (4.6)	1 (0.76)	7 (2.7)	.13[b]
Readjustment counseling	9 (6.9)	7 (5.3)	16 (6.1)	.75[b]

Abbreviation: VA, Veterans Administration.
[a] VA compensation and pension boards rule on the presence or absence of a VA service-connected disability. The disability may be related to medical or psychiatric disorders. The extent of disability ranges from 0% to 100%.
[b] Fisher exact test.
[c] *t* Test.
[d] Data were missing for 60 patients.
[e] Data were missing for 42 patients.

Retention

Rates of retention while receiving randomized treatment were high and did not differ by group (log-rank test $\chi^2_1=0.71$, $P=.40$) (eFigure 1). However, patients treated with placebo continued receiving assigned medication on average approximately 1 week longer than patients treated with risperidone (risperidone: median, 166.5 days; mean, 133.1 days; 95% confidence interval [CI], 123.6-142.6 days; placebo: median, 167.0 days; mean, 148.9 days; 95% CI, 141.5-156.4 days; $t=2.59$; Satterthwaite $df=238.87$; $P=.01$).

Treatment Effects

There were no significant effects of risperidone treatment on the primary outcome measure, the change in CAPS total score from baseline to 24 weeks (risperidone: –16.3; 95% CI, –19.7 to –12.9; placebo: –12.5; 95% CI, –15.7 to –9.4; mean difference, 3.74; 95% CI, –0.86 to 8.35; $t=1.6$; $P=.11$). In the mixed model of CAPS total scores, the effect of medication was also not significant ($F_{1,253}=2.30$; $P=.13$), but symptom scores decreased over time in both groups ($F_{2,488}=9.94$; $P<.001$) (FIGURE 2 and TABLE 4). Baseline CAPS score ($F_{1,\ 253}=257.67$; $P<.001$), but not the war in which the veteran served, was associated with higher CAPS score throughout the study. Neither effect interacted significantly with medication group and controlling for their effects did not alter the findings.

To further explore whether risperidone produced clinically significant changes on the CAPS, the distribution of patients in each treatment group was determined following a published categorization of PTSD status[32] (0-19, asymptomatic/few symptoms; 20-39, mild PTSD/subthreshold; 40-59, moderate PTSD/threshold; 60-79, severe PTSD symptomatology; and >80, extreme PTSD symptomatology). This

analysis did not reveal significant differences across treatment groups (χ^2_4=4.9; P=.30). This analysis also provided information about the rate of remission of patients in each group because a CAPS score of less than 20 is a validated remission threshold.[38] The rate of remission in patients treated with placebo (4%) did not differ significantly from patients treated with risperidone (5%) (eFigure 2).

In post hoc Bonferroni-adjusted analyses (P=.02) of CAPS subscales using mixed regression models, risperidone was associated with significantly reduced symptoms as measured by the CAPS reexperiencing subscale ($F_{1,253}$=8.16, P=.005, d=0.298) and the CAPS hyperarousal subscale (treatment: $F_{1,253}$=8.09, P=.005, d=0.318; treatment × week interaction: $F_{2,486}$=4.11, P=.02), but not the CAPS avoidance/numbing subscale ($F_{1,253}$=1.23, P=.27). Assuming a 0.5-SD threshold for the minimal clinically important difference, the statistically significant findings for the CAPS subscales do not meet this threshold. This suggests that although statistically significant, the changes on the CAPS scales would not be recognized by many clinicians as meaningful.

Consistent with the CAPS findings, no medication effects on the observer-rated version (χ^2_1=3.88, P=.049) or self-rated version (χ^2_1=1.88, P=.17) of the CGI were significant after Bonferroni adjustments for multiple comparisons (significance threshold: P=.008). Also there were no significant drug effects on anxiety (HAMA score: $F_{1,249}$=3.20, P=.08), depression (MADRS score: $F_{1,248}$=2.02, P=.16), psychosis (PANSS positive symptom score: $F_{1,250}$=0.43, P>.10), or quality of life (SF-36V physical component score: $F_{1,248}$=2.24, P=.14).

Table 3. Mental Health Conditions and Measures at Baseline

	No. (%)			
	Risperidone (n = 133)	Placebo (n = 134)	Total (N = 267)	*P* Value
PTSD symptom attribution				
Direct participation in combat	108 (81.2)	101 (75.4)	209 (78.3)	.70[a]
Other combat-related events	12 (9.0)	17 (12.7)	29 (10.9)	
Physical or sexual abuse	7 (5.3)	8 (6.0)	15 (5.6)	
Other event during military service	6 (4.5)	8 (6.0)	14 (5.2)	
Alcohol[b,c]				
Absent	46 (34.6)	53 (39.6)	99 (37.1)	.67[a]
Abuse	27 (20.3)	24 (17.9)	51 (19.1)	
Dependence	60 (45.1)	56 (41.8)	116 (43.4)	
Cannabis[b,c]				
Absent	98 (73.7)	103 (76.9)	201 (75.3)	.67[a]
Abuse	20 (15.0)	15 (11.2)	35 (13.1)	
Dependence	15 (11.3)	15 (11.2)	30 (11.2)	
Cocaine[b,c]				
Absent	111 (83.5)	107 (79.9)	218 (81.6)	.77[a]
Abuse	10 (7.5)	10 (7.5)	20 (7.5)	
Dependence	12 (9.0)	16 (11.9)	28 (10.5)	
No. of cigarettes per day[c]				
0	86 (64.7)	92 (68.7)	178 (66.7)	.51[a]
≥1	47 (35.3)	41 (30.6)	88 (33.0)	
Major depression[b,c]				
Absent	34 (25.6)	31 (23.1)	65 (24.3)	.65[a]
Subthreshold	9 (6.8)	6 (4.5)	15 (5.6)	
Threshold	90 (67.7)	96 (71.6)	186 (69.7)	
Dysthymia[b,c]				
Absent	116 (87.2)	115 (85.8)	231 (86.5)	.70[a]
Subthreshold	5 (3.8)	3 (2.2)	8 (3.0)	
Threshold	12 (9.0)	15 (11.2)	27 (10.1)	
Generalized anxiety disorder[b,c]				
Absent	113 (85.0)	117 (87.3)	230 (86.1)	.77[a]
Subthreshold	5 (3.8)	4 (3.0)	9 (3.4)	
Threshold	15 (11.3)	12 (9.0)	27 (10.1)	
Social phobia[b,c]				
Absent	122 (91.7)	123 (91.8)	245 (91.8)	>.99[a]
Subthreshold	6 (4.5)	6 (4.5)	12 (4.5)	
Threshold	5 (3.8)	4 (3.0)	9 (3.4)	
Antisocial personality disorder[b]				
Absent	119 (89.5)	125 (93.3)	244 (91.4)	.20[a]
Subthreshold	4 (3.0)	1 (0.7)	5 (1.9)	
Threshold	10 (7.5)	6 (4.5)	16 (6.0)	
Missing data	0	2 (1.5)	2 (0.7)	

(continued)

Adverse Events

Adverse events that occurred in at least 5% of the overall sample are reported in eTable 5. Overall, the rate of adverse events during treatment was low but appeared related to dosing of risperidone. The study protocol targeted a risperidone dose of 3 mg/day and allowed clinicians to increase the dose to 4 mg if indicated. With these instructions, the modal medication dose was 4 mg for both groups. By the end of the study, patients randomized to receive placebo were receiving 3.35 mg of placebo on average, suggesting that clinicians were satisfied with the clinical progress of many patients treated with placebo. However, patients randomized to risperidone were receiving on average a dose of 2.74 mg. This suggests, consistent with our clinical impressions, that adverse effects limited some patients from achieving the target dose of 3 mg. This study was unable to determine whether adverse effects limited the efficacy of risperidone, but perhaps these data suggest that future studies should explore doses lower than 3 mg of risperidone.

However, there were significantly more cases in the group treated with risperidone of self-reported weight gain (risperidone: n=20, 15.3%; placebo: n=3, 2.3%), fatigue (risperidone: n=18, 13.7%; placebo: n=0), somnolence (risperidone: n=13, 9.9%; placebo: n=2, 1.5%), and hypersalivation (risperidone: n=13, 9.9%; placebo: n=1, 0.8%) (eTable 5). Risperidone did not increase measured weight significantly ($F_{1,235}$=2.86, P=.09). Also, there were no significant effects of risperidone on the 3 measures of extrapyramidal symptoms in this study, the Barnes Akathisia Scale, the Extrapyramidal Symptom Rating Scale, and the Abnormal Involuntary Movement Scale.

Table 3. Mental Health Conditions and Measures at Baseline (continued)

	No. (%)			
	Risperidone (n = 133)	Placebo (n = 134)	Total (N = 267)	*P* Value
CAPS score, mean (SD)				
Total	78.2 (15.0)	78.2 (14.7)	78.2 (14.8)	>.99[d]
Part B (reexperiencing)	20.9 (6.6)	20.8 (6.2)	20.9 (6.4)	.83[d]
Part C (avoidance/numbing)	31.1 (8.1)	31.9 (8.1)	31.5 (8.1)	.40[d]
Part D (hyperarousal)	26.2 (5.1)	25.5 (4.7)	25.9 (4.9)	.27[d]
PCL score, mean (SD)				
Total[e]	64.1 (10.6)	63.6 (11.7)	63.9 (11.2)	.72[d]
Part B (reexperiencing)[f]	18.2 (4.1)	18.4 (4.2)	18.3 (4.1)	.69[d]
Part C (avoidance/numbing) [g]	25.8 (5.2)	25.6 (5.6)	25.7 (5.4)	.71[d]
Part D (hyperarousal)[h]	19.9 (3.4)	19.4 (4.0)	19.7 (3.7)	.26[d]
CGI, observer rated, mean (SD)[f]	5.1 (0.9)	5.0 (0.9)	5.0 (0.9)	.08[d]
MADRS, mean (SD)[i]	24.3 (7.3)	22.5 (9.0)	23.4 (8.2)	.08[d]
HAMA, mean (SD)[j]	19.7 (8.1)	19.2 (7.5)	19.4 (7.8)	.60[d]
PANSS score, mean (SD)[f]				
Total	59.4 (13.8)	59.4 (14.3)	59.4 (14.1)	.97[d]
Positive symptoms	11.5 (3.7)	11.7 (4.2)	11.6 (3.9)	.62[d]
Negative symptoms	14.0 (4.7)	13.7 (4.9)	13.9 (4.8)	.67[d]
General	33.9 (7.6)	34.0 (7.8)	34.0 (7.7)	.94[d]
Pittsburgh Sleep Scale total score, mean (SD)[k]	13.8 (3.9)	13.6 (3.9)	13.7 (3.9)	.77[d]
BLSI score, mean (SD)[l]	101.5 (25.5)	104.4 (29.6)	102.9 (27.6)	.41[d]
SF-36V PCS score, mean (SD)[m]	30.3 (9.8)	31.3 (11.3)	30.8 (10.6)	.44[d]
SF-36V MCS score, mean (SD)[m]	39.2 (11.8)	39.7 (10.6)	39.5 (11.2)	.69[d]

Abbreviations: BLSI, Boston Life Satisfaction Inventory; CAPS, Clinician-Administered PTSD Scale; CGI, Clinical Global Impression; HAMA, Hamilton Anxiety Scale; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PCL, PTSD Checklist; PTSD, posttraumatic stress disorder; SF-36V PCS and MCS, Veterans RAND 36-Item Health Survey physical component subscale and mental component subscale.
[a] Fisher exact test.
[b] Based on lifetime *DSM-IV* diagnosis.
[c] Data were missing or incorrect for 1 patient in the placebo group (0.4% of total patients).
[d] *t* Test.
[e] Data were missing for 13 patients.
[f] Data were missing for 1 patient.
[g] Data were missing for 10 patients.
[h] Data were missing for 7 patients.
[i] Data were missing for 2 patients.
[j] Data were missing for 3 patients.
[k] Data were missing for 23 patients.
[l] Data were missing for 18 patients.
[m] Data were missing for 4 patients.

COMMENT

In this study, there was no statistically significant difference between risperidone and placebo in reducing CAPS total scores when prescribed for 6 months as an adjunct to SRIs and other ongoing medication and psychosocial treatments in a group of highly symptomatic veterans with medication-resistant symptoms associated with chronic military-related PTSD. Compared with placebo, risperidone produced only a 3.74-point greater reduction from baseline in the CAPS total score. Thus, it is unlikely that clinicians could detect the magnitude of the risperidone effect over placebo that was observed in this study. In addition, risperidone was not statistically superior to placebo on any of the secondary outcomes, including the observer- and self-rated versions of the Clinical Global Impressions scale; quality of life (SF-36V or BLSI); and measures of depression (MADRS), anxiety (HAMA), or paranoia/psychosis (PANSS positive symptom subscale).

Adverse events associated with risperidone were not serious. Post hoc analyses of the CAPS, adjusted for multiple comparisons, suggested that risperidone was associated with a significant reduction in reexperiencing and hyperarousal symptoms associated with PTSD with a small effect size. Although the findings were significant statistically, these changes were smaller than the 0.5-SD threshold used to define the minimal important difference in estimating the sample size for this study.[34] Thus, it is questionable whether the observed changes on these subscales would be detected clinically.

However, this study could not rule out the possibility that risperidone treatment addressed a real clinical need for some patients. The ability of risperidone to reduce reexperiencing and hyperarousal symptoms, such as disrupted sleep and autonomic arousal, is consistent with its ability to block 5-HT_{2A} and α_1 adrenergic receptors.[39] This hypothesis is supported by the widespread prescription of trazodone, a 5-HT_2 receptor antagonist, for sleep impairment associated with PTSD.[40] It is also consistent with the increasing evidence of the efficacy of prazosin, an α_1 adrenergic receptor antagonist, for treating reexperiencing and hyperarousal symptoms of PTSD.[41-43]

The lack of efficacy of adjunctive risperidone on CAPS total scores and global outcome measures in this study contrasts with positive findings from some smaller randomized trials[4-11,44] but is consistent with a study of SRI-resistant civilian PTSD.[45] However, the lack of risperidone efficacy on avoidance/emotional numbing symptoms

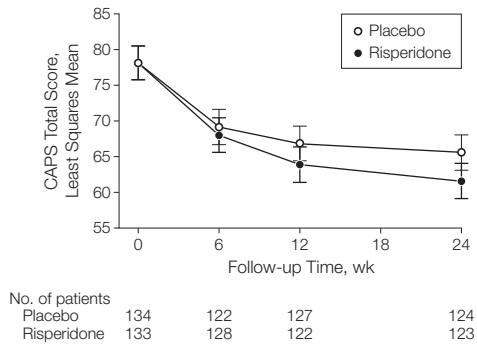
Table 4. Follow-up Assessment Outcomes Based on Least Squares Mean Estimates With All Available Data Up to 24 Weeks[a]

Variable	Mean (95% CI)		Mean Difference (95% CI)	*P* Value
	Risperidone	Placebo		
CAPS score				
Total	64.43 (61.98 to 66.89)	67.16 (64.71 to 69.62)	2.73 (–0.74 to 6.20)	.12
Part B (reexperiencing)	15.54 (14.58 to 16.49)	17.55 (16.60 to 18.50)	2.01 (0.66 to 3.37)	.004
Part C (avoidance/numbing)	27.98 (26.77 to 29.19)	26.93 (25.72 to 28.13)	–1.05 (–2.76 to 0.66)	.23
Part D (hyperarousal)	20.99 (20.16 to 21.83)	22.70 (21.87 to 23.54)	1.71 (0.53 to 2.89)	.005
HAMA	15.80 (14.86 to 16.75)	16.97 (16.02 to 17.92)	1.16 (–0.18 to 2.51)	.09
MADRS	19.24 (18.19 to 20.29)	20.43 (19.39 to 21.48)	1.19 (–0.29 to 2.68)	.11
BLSI	104.62 (102.02 to 107.22)	104.30 (101.64 to 106.95)	–0.32 (–4.04 to 3.40)	.87
SF-36V PCS	39.66 (38.63 to 40.68)	38.53 (37.50 to 39.55)	–1.13 (–2.58 to 0.32)	.13
SF-36V MCS	33.80 (32.48 to 35.13)	33.55 (32.22 to 34.87)	–0.26 (–2.13 to 1.61)	.79
PANSS score				
Total	55.77 (54.24 to 57.30)	55.56 (54.03 to 57.09)	–0.21 (–2.37 to 1.96)	.85
General symptoms	31.69 (30.81 to 32.56)	31.80 (30.93 to 32.68)	0.12 (–1.12 to 1.35)	.85
Positive symptoms	10.65 (10.26 to 11.05)	10.85 (10.46 to 11.25)	0.20 (–0.35 to 0.75)	.48
Negative symptoms	13.45 (12.96 to 13.94)	12.88 (12.39 to 13.37)	–0.57 (–1.26 to 0.13)	.11
CGI, patient rated	4.49 (4.30 to 4.67)	4.68 (4.50 to 4.86)	0.20 (–0.06 to 0.45)	.14
CGI, observer rated	4.32 (4.20 to 4.43)	4.49 (4.38 to 4.61)	0.18 (0.01 to 0.34)	.04
Weight, lb	211.86 (210.48 to 213.25)	210.18 (208.78 to 211.58)	–1.68 (–3.66 to 0.29)	.09

Abbreviations: BLSI, Boston Life Satisfaction Inventory; CAPS, Clinician-Administered PTSD Scale; CGI, Clinical Global Impression; CI, confidence interval; HAMA, Hamilton Anxiety Scale; MADRS, Montgomery-Asberg Depression Rating Scale; PANSS, Positive and Negative Syndrome Scale; PTSD, posttraumatic stress disorder; SF-36V PCS and MCS, Veterans RAND 36-Item Health Survey physical component subscale and mental component subscale.

[a]For all outcomes, the treatment comparison was a linear contrast based on a mixed-effects model with site as a random effect and with autocorrelated repeated measures over time. On all reported outcome measures except SF-36V, higher scores reflect higher symptom levels; higher scores on SF-36V reflect higher quality of life.

Figure 2. Change in CAPS Total Score During Treatment



CAPS indicates Clinician-Administered Posttraumatic Stress Disorder Scale. Error bars indicate 95% confidence intervals.

and the relatively greater efficacy for hyperarousal or reexperiencing symptoms appear to be consistent with findings of prior risperidone studies.[12] Second-generation antipsychotics have been proposed as a treatment strategy for paranoia or other psychotic symptoms associated with PTSD.[46,47] However, positive symptoms of psychosis were at very low levels at baseline in this study. Thus, this study does not inform the question of whether risperidone would be a useful adjunct to treatment in paranoid or psychotic patients with PTSD.

This study has several limitations. This study did not achieve the prespecified sample size of 410 patients projected for this study. Further, source documentation for 29 patients was inadvertently lost, invalidating their data. These 29 patients (9.8% of all randomized study participants) were enrolled at 2 of the original study sites. After the loss of data was discovered, the 29 patients were excluded from further analyses and enrollment was discontinued at both sites. At 1 of these sites, enrollment was later restarted with a new site investigator. Because our analyses controlled for clustering by study site, it is unlikely that the loss of patient data from these 2 sites would have biased the results, which were based only on patient data from the 23 other study sites. In addition, the study participants in these 2 sites were balanced with respect to treatment group (14 in the risperidone group and 15 in the placebo group), so pre-existing biases were likely to have been distributed equally across treatment groups. Even after excluding these 29 patients, our study had adequate statistical power to detect a clinically meaningful benefit of risperidone, if a true benefit had existed.

Patient retention in the study was greater than expected and variance within the data was less than expected. Based on the 247 patients who completed the study and the prespecified factors in the power analysis, this study had 96.6% power to detect a

9-point difference in the ability of risperidone and placebo to reduce CAPS total score during treatment, a change that might be considered a minimal important difference. However, even if the full projected sample had been recruited, this study most likely would not have yielded statistical significance for the small differential change in CAPS total scores produced by risperidone and placebo (3.74 points).

A second limitation is that study entry criteria were relaxed because of recruitment problems; patients were accepted who had long-standing prescriptions of low doses of commonly prescribed sleep medications, particularly trazodone and quetiapine. Although adjusting for this effect did not alter the findings with respect to the CAPS, including these patients may have reduced the expected effects of risperidone in the current study. Third, it is not clear that the findings generalize to other SGAs, such as olanzapine or quetiapine, that may have somewhat different clinical profiles in PTSD.[10] Fourth, it remains to be determined whether the findings generalize to women because the study population was nearly entirely men. Analyses conducted to adjust for the effect of differing combat theaters did not alter the findings related to the primary outcome measure, but this study was not designed explicitly to explore the interaction of combat theater and treatment response. Fifth, this study evaluated the efficacy of adjunctive risperidone treatment, and the findings may not generalize to risperidone prescribed by itself for the treatment of PTSD.

In summary, risperidone, the second most widely prescribed SGA within VA for PTSD and the best data-supported adjunctive pharmacotherapy for PTSD,[12] did not reduce overall PTSD severity (CAPS total score), produce global improvement (CGI score), or increase quality of life (SF-36V) in patients with chronic SRI-resistant military-related PTSD symptoms. Overall, the data do not provide strong support for the current widespread prescription of risperidone to patients with chronic SRI-resistant military-related PTSD symptoms, and these findings should stimulate careful review of the benefits of these medications in patients with chronic PTSD.

Author Affiliations: Clinical Neuroscience Division, Department of Veterans Affairs National Center for PTSD (Dr Krystal), and Psychiatry Service, VA Connecticut Healthcare System, West Haven (Drs Krystal and Rosenheck and Mss Cramer and Vessicchio); Department of Psychiatry, Yale University School of Medicine, New Haven, Connecticut (Drs Krystal and Rosenheck and Mss Cramer and Vessicchio); Psychiatry Services, Yale–New Haven Hospital, New Haven (Dr Krystal); VA New England Mental Illness Research Education and Clinical Center, West Haven (Dr Rosenheck); VA Cooperative Studies Program Coordinating Center, Perry Point, Maryland (Mss Jones and Horney); VA Cooperative Studies Program Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico (Dr Vertrees); Cooperative Studies Program Central Office, VA Office of Research and Development, Washington, DC (Dr Huang); and Pharmacy Department/Mental Health Service, VA Medical Center, Salt Lake City, Utah (Dr Stock).

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Study concept and design: Krystal, Rosenheck, Cramer, Jones, Vertrees.
Acquisition of data: Rosenheck, Cramer, Vessicchio, Stock.
Analysis and interpretation of data: Krystal, Rosenheck, Jones, Vertrees, Horney, Huang.
Drafting of the manuscript: Krystal, Rosenheck, Huang.
Critical revision of the manuscript for important intellectual content: Krystal, Rosenheck, Cramer, Vessicchio, Jones, Vertrees, Horney, Huang, Stock.
Statistical analysis: Krystal, Rosenheck, Jones, Horney.
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Members of the Department of Veterans Affairs Cooperative Study No. 504 Group (in addition to the authors): J. Canive, L. Calais, A. Smith, E. Nye, Albuquerque, New Mexico; E. Duncan, K. Skelton, R. Bradley, K. Tabb, T. Sergent, M. Daugherty, E. Russ, Atlanta, Georgia; N. Denny, K. Arnemann, J. Lauren-Rusnack, J. Schillac, Austin, Texas; S. Batten, L. Dixon, A. Santanello, L. Bell, J. Duncan, S. Carney, G. Kavanagh, Baltimore, Maryland; P. Parker, K. McCall, S. Rathmell, Birmingham, Alabama; D. Kaloupek, G. Aguayo, D. Ryngala, A. Collins, Boston, Massachusetts; M. Hamner, D. Agbor-Tabi, M. Timmerman, M. Brown, S. Robert, S. Coleman, Charleston, South Carolina; P. Fore, T. Tepper, J. Yount, Chicago, Illinois; E. Konicki, V. Nero, E. Smith, R. Huhra-Grassel, Cleveland, Ohio; A. Suris, C. North, J. Whitman, E. Wiley, Dallas, Texas; M. Hertzberg, R. Biddix, M. Becker, Durham, North Carolina; T. Grieder, C. Feigel, East Los Angeles, California; T. Vo, P. Wolf, Fargo, North Dakota; R. Garza, C. Murphy, B. Melton, Houston, Texas; E. Ahearn, C. Johnson, M. Mussey, T. Smith, Madison, Wisconsin; D. David, J. Junco-Valladares, P. Slone, A. Giron, Miami, Florida; J. Westermeyer, M. Spring, A. Ferrier, Minneapolis, Minnesota; M. Eakin, A. Wolkin, C. Woo, M. Kramer, New York, New York; R. Erhman, K. Marquez, A. Fornish, Philadelphia, Pennsylvania; A. Khan, A. Zakai, H. Frank, J. Kikuchi, Providence, Rhode Island; C. Stock, L. Carpenter, S. Plumb, S. Allen, C. Olsen, M. Greenwell, Salt Lake City, Utah; J. Casada, J. Polanco, T. Benson, San Antonio, Texas; D. Baker, P. Shah, P. Gorman, T. Perin, A. Kelada, J. Cooley, J. Pittman, N. Madra, San Diego, California; F. Schoenfeld, M. Schmitz, R. Coeshott, H. Q. Tong, San Francisco, California; L. Davis, C. Garner, J. Newell, Tuscaloosa, Alabama; P. Hicks, S. Justice, B. Lippe, Waco, Texas; C. S. Saunders, D. Goldstein, S. Ereshefsky, A. Melnick, M. Urbaitis, West Los Angeles, California; S. Affleck, M. Beam, E. Spence, D. Briones, S. Dixon, C. Howell, X. Lu, Perry Point, Maryland; D. Conner, C. Haakenson, Albuquerque. *Data Monitoring Committee*: T. Grieger, Falls Church, VA; D. Blake, Boise, ID; K. Dickerson, Baltimore; M. Thase, Philadelphia; P. Harvey, Miami. *Executive Committee:* K. Jones, Perry Point; J. Vertrees, Albuquerque; M. Stein, San Diego; C. Stock, Salt Lake City; M. Hertz-

berg, Durham; E. Duncan, Atlanta; J. Gelernter, New Haven, Connecticut. *Planning Committee:* D. Ciraulo, D. Kaloupek, Boston; M. Stein, San Diego; G. Bartzokis, Los Angeles; A. Rasmusson, West Haven, Connecticut; J. Davidson, Durham; C. Marmar, San Francisco; P. Lavori, Menlo Park, California; S. Berkowitz, T. O'Leary, B. Schuster, Washington, DC; K. Jones, J. Collins, C. Howell, Perry Point; J. Vertrees, Albuquerque; D. Bradham, Baltimore; M. Friedman, White River Junction, Vermont.

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