Sleep Disturbance in Chronic Military-Related PTSD: Clinical Impact and Response to Adjunctive Risperidone in the Veterans Affairs Cooperative Study #504

John H. Krystal, MD[a,b,c,d,e,*]; Robert H. Pietrzak, PhD, MPH[a,c]; Robert A. Rosenheck, MD[b,c]; Joyce A. Cramer, BS[b,c]; Jennifer Vessicchio, MSW[b,c]; Karen M. Jones, MS[f]; Grant D. Huang, MPH, PhD[g]; Julia E. Vertrees, PharmD[h]; Joseph Collins, ScD[f]; and Andrew D. Krystal, MD[i]; for the Veterans Affairs Cooperative Study #504 Group

ABSTRACT

Objective: Sleep disturbances are common among veterans with chronic military-related posttraumatic stress disorder (PTSD). This article reports the results of a multicenter clinical trial that explored the clinical correlates of reported sleep impairment in these veterans and tested the impact of the second-generation antipsychotic risperidone upon these symptoms.

Method: This article reports secondary analyses of a 24-week multicenter randomized placebo-controlled trial of adjunctive risperidone in patients with chronic military-related PTSD symptoms (n = 267, 97% male) who were symptomatic despite treatment with antidepressants and other medications. The study was conducted between February 2007 and February 2010. *DSM-IV* PTSD diagnoses were made by using the Structured Clinical Interview for *DSM-IV-TR* Axis I Disorders, Nonpatient Edition. Sleep disturbances were assessed principally by using the Pittsburgh Sleep Quality Index (PSQI) (primary outcome measure). Analyses were conducted using bivariate correlations and longitudinal mixed model regressions.

Results: Eighty-eight percent of the patients in this study had clinically significantly impaired sleep on the PSQI. Severity of sleep disturbances correlated with PTSD symptom severity as measured by the Clinician-Administered PTSD Scale (CAPS) and reductions in multiple measures of quality of life (Veterans RAND 36-item Health Survey [SF-36 V] subscales, Boston Life Satisfaction Index). Risperidone produced small but statistically significant effects on total PSQI scores (main effect of drug: $F_{1,228} = 4.57$, $P = .034$; drug-by-time interaction: $F_{2,421} = 4.32$, $P = .014$) and severity of nightmares as assessed by the CAPS (main effect of drug: $F_{1,248} = 4.60$, $P = .033$). The improvements in sleep quality produced by risperidone correlated with reductions in PTSD symptom severity and improvement in the mental health subscale of the SF-36 V.

Conclusions: This study highlighted the near universality and significant negative impact of severe disturbances in sleep quality in veterans with chronic military-related PTSD who were partial responders to standard pharmacotherapies. The modest improvements in sleep quality produced by adjunctive risperidone were correlated with limited reductions in PTSD severity and improvements in quality of life.

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[a]Clinical Neurosciences Division, Department of Veterans Affairs National Center for PTSD, and [b]Psychiatry Service, VA Connecticut Healthcare System, West Haven
[c]Departments of Psychiatry and [d]Neurobiology, Yale University School of Medicine, New Haven, Connecticut
[e]Psychiatry Services, Yale-New Haven Hospital, Connecticut
[f]VA Cooperative Studies Coordinating Center, Perry Point, Maryland
[g]Cooperative Studies Program Central Office, VA Office of Research and Development, Washington, DC
[h]VA Cooperative Studies Clinical Research Pharmacy Coordinating Center, Albuquerque, New Mexico
[i]Sleep Disorders Center, Department of Psychiatry, Duke University School of Medicine, Durham, North Carolina
**Corresponding author:* John H. Krystal, MD, Clinical Neurosciences Division, VA National Center for PTSD, VA Connecticut Healthcare System (151-D) 950 Campbell Ave, West Haven, CT 06516 (john.krystal@yale.edu).

Sleep disturbances are common among people with posttraumatic stress disorder (PTSD) arising from combat[1–4] and sexual assault or military sexual trauma.[5–7] In military personnel returning from deployment in Iraq and Afghanistan, sleep impairment is the most common and severe PTSD symptom.[8] In Vietnam War veterans, combat was most closely associated with nightmares, less commonly associated with delayed sleep onset, and infrequently associated with reduced sleep maintenance.[9] Polysomnographic studies also yield objective evidence of impaired sleep in PTSD.[2,10–15]

Sleep disturbances contribute importantly to PTSD-related impairments in quality of life, function, and health.[16] In a sample of 1,200 police officers, the severity of sleep disturbances, as measured by the Pittsburgh Sleep Quality Index (PSQI), partially mediated the relationship between PTSD symptoms and somatic symptoms and completely mediated the relationship between PTSD symptoms and health function, as measured by the 12-item Short-Form Health Survey (SF-12).[17] Further, sleep disturbances associated with PTSD may also be a marker for reductions in cortical[18] and hippocampal[19] volumes measured with structural neuroimaging, yielding an additional path through which impairments in sleep and function might be related.

The treatment of sleep disturbances associated with PTSD is evolving. Cognitive and behavioral therapy approaches are helpful with PTSD-related sleep disturbances and nightmares, in particular.[20–24] Sleep disturbances are linked to the underlying neurobiology of PTSD,[25] suggesting that pharmacotherapy would be helpful. However, sleep disturbances measured by the PSQI did not improve in a multicenter study[26] of sertraline, a pharmacotherapy for PTSD approved by the US Food and Drug Administration (FDA). Similar results were observed in veterans treated with fluoxetine.[27] Because of the equivocal evidence for the

efficacy of the FDA-approved serotonin reuptake inhibitor (SRI) antidepressants for sleep disturbance in PTSD, other medications have been explored for this purpose, particularly α_1 adrenergic antagonists, such as prazosin,[28,29] and serotonin-2 (5-HT_2) receptor antagonists, including cyproheptadine, trazadone, and nefazadone.[30–33] Second-generation antipsychotics, including risperidone, olanzapine, and quetiapine, also have been reported to have varying degrees of efficacy for PTSD-related sleep disturbance.[34–38]

The current study examined the prevalence and clinical impact of sleep disturbances in a sample of 267 veterans with chronic military-related PTSD who remained symptomatic despite SRI treatment and who participated in a clinical trial conducted in 26 US Department of Veterans Affairs (VA) Medical Centers across the United States, VA Cooperative Study #504. Second, in this dataset, we evaluated the efficacy of risperidone at doses of up to 4 mg administered at bedtime for treating impaired sleep in these patients during a 24-week period of randomized treatment under double-blind conditions. The efficacy of risperidone for PTSD symptoms, as measured by the Clinician-Administered PTSD Scale (CAPS), was reported previously.[39]

Clinical Points

- In veterans with chronic military-related posttraumatic stress disorder (PTSD) symptoms, clinically significant sleep impairments are very common despite ongoing psychosocial and pharmacologic treatments.
- Risperidone treatment did not produce an overall effect on PTSD symptoms in veterans with chronic military-related PTSD. However, it produced reductions in their sleep impairment that were associated with limited decreases in PTSD symptoms and improvements in quality of life.
- However, the beneficial effects of risperidone on sleep were both small in magnitude and very delayed in their onset.

METHOD

Participants

The patient sample and study methods were reported previously.[39] 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 diagnostic interview,[40] had a Clinician-Administered PTSD-1 (CAPS-1) score over 50,[41] had a clinical history of intolerance of or nonresponse to 2 or more antidepressants, responded inadequately to an adequate trial (minimum of 4 weeks of pharmacotherapy), had a fixed address within 50 miles of the research site or confirmed transportation for all visits, used an acceptable method of birth control (females), and gave written informed consent.

Patients were excluded if they met lifetime diagnostic criteria for bipolar disorder or schizophrenia, required medication treatment for psychosis, met diagnostic criteria for dependence on a substance other than nicotine in the 30 days prior to screening, had clinical or laboratory evidence 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. While ongoing pharmacotherapy was allowed, second-generation antipsychotics, 5-HT_2 receptor antagonists (cyproheptadine, methysergide, trazodone), α_1 receptor antagonists (prazosin), and α_2 receptor agonists/antagonists (clonidine, guanfacine, mirtazapine) were excluded initially (see Randomization and Medication Treatment).

The Human Subjects Subcommittees of the VA Cooperative Studies Program and each participating VA Medical Center approved this study. The study was conducted between February 2007 and February 2010. The authors were responsible for the collection, management, and analysis of the data and for the preparation of the manuscript and its submission for publication. J.H.K. wrote the first draft. The trial was registered at ClinicalTrials.gov (identifier: NCT00099983).

Interventions

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 double-blinded 24-week treatment with risperidone or matched placebo. Study medication (risperidone 1 mg or placebo) was initiated at a dose of 1 tablet by mouth at bedtime and increased by 1 tablet per week to a dose of 3 tablets at bedtime. After patients were on study medication for 4 weeks, blinded investigators treating patients had the option of 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 provider developed a treatment plan that would not violate study protocol and would be engaged if study medications were ineffective. The extent to which these alternative treatments were employed is reported elsewhere.[39]

Patients participated in a program that was designed to enhance adherence to prescribed medications.[42,43] Medication was provided in bottles with medication event monitoring system (MEMS) caps (AARDEX; 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[42] feedback system encouraged patients to take medication daily by training them to develop and utilize reminders that supported medication adherence. Data on the previous month's dosing were shown to patients at each visit to demonstrate self-efficacy.

Randomization and Medication Treatment

Patients were recruited from 20 VA medical centers over a 2-year period. Subsequently, steps were taken to address low

recruitment rates: (1) 8 sites were discontinued and replaced by 6 new sites, (2) the recruitment period was extended by 6 months, and (3) long-standing doses of drugs initially excluded (trazodone ≤ 100 mg, nefazadone ≤ 100 mg, quetiapine ≤ 25 mg, and mirtazapine ≤ 30 mg) were allowed, provided that the patients had received this medication for at least 3 months and had not changed their dose in the month prior to study entry. Secondary analyses testing the impact of broadening the study entrance 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. Patients were evaluated to assure they met all eligibility criteria before a randomization code was provided. Treatment was initiated within a day of randomization.

Outcome Measures

The primary outcome measure was the total score on the 34-item CAPS.[41] This scale was administered by trained raters at baseline and weeks 6, 12, and 24. The CAPS provided a measure of PTSD symptom severity as well as the severity of the 3 component clusters of PTSD symptoms associated with the *DSM-IV* diagnostic criteria[44]: reexperiencing, avoidance/numbing, and hyperarousal.

The primary outcome measure in this secondary analysis was the PSQI.[45] The PSQI is a 19-item self-report questionnaire that assesses 7 aspects of sleep quality: subjective sleep quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, use of sleep medication, and impairment of daytime functioning. Each component is rated on a 0 to 3 scale. A global sleep quality score, ranging from 0 to 21, is obtained by summing scores from each component scale. Higher scores are indicative of increased sleep difficulties, and a score > 5 is indicative of significantly impaired sleep. In addition to PSQI scores, we analyzed scores on CAPS items assessing trauma-related nightmares (*DSM-IV* criterion B, symptom 2) and sleep difficulties (*DSM-IV* criterion D, symptom 1).

To examine the relation between sleep disturbance and measures of functioning and life satisfaction, the Veterans RAND 36-item Health Survey (SF-36 V)[46] and Boston Life Satisfaction Inventory (BLSI)[47] were administered. Two validated SF-36 V subscales are reported here: the mental component score (MCS) and physical component score (PCS).[48,49] On the SF-36 V and its subscales, lower scores reflect greater impairment. The BLSI is a self-report measure composed of 26

Table 1. Baseline Demographic, Military, and Clinical Characteristics

Variable	Placebo (n = 134)	Risperidone (n = 133)	Total (N = 267)	*P* Value
Age, mean (SD), y	54.5 (10.6)	54.2 (10.8)	54.4 (10.7)	.8208[a]
Gender, n (%)				.7492[b]
Male	130 (97.0)	128 (96.2)	258 (96.6)	
Female	4 (3.0)	5 (3.8)	9 (3.4)	
Race, n (%)				.5669[b]
White, not of Hispanic origin	93 (69.4)	84 (63.2)	177 (66.3)	
Black, not of Hispanic origin	25 (18.7)	25 (18.8)	50 (18.7)	
Hispanic	11 (8.2)	16 (12.0)	27 (10.1)	
Other	5 (3.7)	8 (6.0)	13 (4.9)	
Marital status, n (%)				.2903[b]
Single	19 (14.2)	20 (15.0)	39 (14.6)	
Married	73 (54.5)	67 (50.4)	140 (52.4)	
Widowed	2 (1.5)	0 (0.0)	2 (0.7)	
Divorced	24 (17.9)	36 (27.1)	60 (22.5)	
Separated	10 (7.5)	5 (3.8)	15 (5.6)	
Living with partner	5 (3.7)	5 (3.8)	10 (3.7)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Education (missing, n = 2), mean (SD), y	14.1 (2.2)	14.2 (2.7)	14.1 (2.5)	.8158[a]
Employment (current), n (%)				.9376[b]
Full time	48 (35.8)	49 (36.8)	97 (36.3)	
Part time	4 (3.0)	6 (4.5)	10 (3.7)	
Irregular, part time	7 (5.2)	7 (5.3)	14 (5.2)	
Unemployed	21 (15.7)	17 (12.8)	38 (14.2)	
Other	53 (39.6)	54 (40.6)	107 (40.1)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Military history, n (%)				.6736[b]
WWI, WWII, Korea, Vietnam	98 (73.1)	95 (71.4)	193 (72.3)	
Gulf War, Afghanistan, Iraq	29 (21.6)	34 (25.6)	63 (23.6)	
Balkans, other	3 (2.2)	1 (0.8)	4 (1.5)	
Peacetime	4 (3.0)	3 (2.3)	7 (2.6)	
Patient receives VA disability, n (%)				.8692[b]
Yes	111 (82.8)	112 (84.2)	223 (83.5)	
No	23 (17.2)	21 (15.8)	44 (16.5)	
Medical service–connected disability, n (%)				.7642[b]
No	31 (27.9)	29 (25.9)	60 (26.9)	
Yes	80 (72.1)	83 (74.1)	163 (73.1)	
Medical disability (missing, n = 60), mean (SD), %	31.8 (23.5)	34.5 (31.8)	33.2 (28.0)	.5454[a]
Psychiatric service-connected disability, n (%)				.6079[b]
No	19 (17.1)	23 (20.5)	42 (18.8)	
Yes	92 (82.9)	89 (79.5)	181 (81.2)	
Psychiatric disability (missing, n = 42), mean (SD), %	65.3 (25.2)	63.4 (28.1)	64.4 (26.6)	.6231[a]
Social Security pension, n (%)				.8995[b]
Yes	49 (36.6)	50 (37.6)	99 (37.1)	
No	85 (63.4)	83 (62.4)	168 (62.9)	
PTSD symptoms attributable to, n (%)				.7014[b]
Direct participation in combat	101 (75.4)	108 (81.2)	209 (78.3)	
Other combat-related events	17 (12.7)	12 (9.0)	29 (10.9)	
Physical or sexual abuse	8 (6.0)	7 (5.3)	15 (5.6)	
Other event during military service	8 (6.0)	6 (4.5)	14 (5.2)	
Alcohol, n (%)[c]				.6680[b]
Absent	53 (39.6)	46 (34.6)	99 (37.1)	
Abuse	24 (17.9)	27 (20.3)	51 (19.1)	
Dependence	56 (41.8)	60 (45.1)	116 (43.4)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Cannabis, n (%)[c]				.6700[b]
Absent	103 (76.9)	98 (73.7)	201 (75.3)	
Abuse	15 (11.2)	20 (15.0)	35 (13.1)	
Dependence	15 (11.2)	15 (11.3)	30 (11.2)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Cocaine, n (%)[c]				.7678[b]
Absent	107 (79.9)	111 (83.5)	218 (81.6)	
Abuse	10 (7.5)	10 (7.5)	20 (7.5)	
Dependence	16 (11.9)	12 (9.0)	28 (10.5)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	

(continued)

Table 1 (continued). Baseline Demographic, Military, and Clinical Characteristics

Variable	Placebo (n = 134)	Risperidone (n = 133)	Total (N = 267)	*P* Value
No. of cigarettes/d, n (%)				.5148[b]
0	92 (68.7)	86 (64.7)	178 (66.7)	
≥ 1	41 (30.6)	47 (35.3)	88 (33.0)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Major depression, n (%)[c]				.6497[b]
Absent	31 (23.1)	34 (25.6)	65 (24.3)	
Subthreshold	6 (4.5)	9 (6.8)	15 (5.6)	
Threshold	96 (71.6)	90 (67.7)	186 (69.7)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Dysthymia, n (%)[c]				.6992[b]
Absent	115 (85.8)	116 (87.2)	231 (86.5)	
Subthreshold	3 (2.2)	5 (3.8)	8 (3.0)	
Threshold	15 (11.2)	12 (9.0)	27 (10.1)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Generalized anxiety disorder, n (%)[c]				.7745[b]
Absent	117 (87.3)	113 (85.0)	230 (86.1)	
Subthreshold	4 (3.0)	5 (3.8)	9 (3.4)	
Threshold	12 (9.0)	15 (11.3)	27 (10.1)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Social phobia, n (%)[c]				1.0000[b]
Absent	123 (91.8)	122 (91.7)	245 (91.8)	
Subthreshold	6 (4.5)	6 (4.5)	12 (4.5)	
Threshold	4 (3.0)	5 (3.8)	9 (3.4)	
Missing/error	1 (0.7)	0 (0.0)	1 (0.4)	
Antisocial personality disorder, n (%)[c]				.1998[b]
Absent	125 (93.3)	119 (89.5)	244 (91.4)	
Subthreshold	1 (0.7)	4 (3.0)	5 (1.9)	
Threshold	6 (4.5)	10 (7.5)	16 (6.0)	
Missing/error	2 (1.5)	0 (0.0)	2 (0.7)	
Weight (missing, n = 13), mean (SD), lb	214.0 (46.1)	205.3 (38.8)	209.6 (42.7)	.1061[a]
CAPS score, mean (SD)	78.2 (14.7)	78.2 (15.0)	78.2 (14.8)	.9960[a]
Criterion B (reexperiencing symptoms), mean (SD)	20.8 (6.2)	20.9 (6.6)	20.9 (6.4)	.8348[a]
Criterion C (avoidance and numbing symptoms), mean (SD)	31.9 (8.1)	31.1 (8.1)	31.5 (8.1)	.4042[a]
Criterion D (hyperarousal symptoms), mean (SD)	25.5 (4.7)	26.2 (5.1)	25.9 (4.9)	.2655[a]
CGI (clinician rated) (missing, n = 1), mean (SD)	5.0 (0.9)	5.1 (0.9)	5.0 (0.9)	.0794[a]
MADRS (missing, n = 2), mean (SD)	22.5 (9.0)	24.3 (7.3)	23.4 (8.2)	.0760[a]
HARS (missing, n = 3), mean (SD)	19.2 (7.5)	19.7 (8.1)	19.4 (7.8)	.6007[a]
PANSS total score (missing, n = 1), mean (SD)	59.4 (14.3)	59.4 (13.8)	59.4 (14.1)	.9725[a]
PSQI total score (missing, n = 23), mean (SD)	13.6 (3.9)	13.8 (3.9)	13.7 (3.9)	.7657[a]
Boston Life Satisfaction Inventory (missing, n = 18), mean (SD)	104.4 (29.6)	101.5 (25.5)	102.9 (27.6)	.4054[a]
SF-36 V PCS (missing, n = 4), mean (SD)	31.3 (11.3)	30.3 (9.8)	30.8 (10.6)	.4401[a]
SF-36 V MCS (missing, n = 4), mean (SD)	39.7 (10.6)	39.2 (11.8)	39.5 (11.2)	.6913[a]

[a] *t* Test.
[b] Fisher test.
[c] Based on lifetime *DSM-IV* diagnosis.
Abbreviations: CAPS = Clinician-Administered PTSD Scale; CGI = Clinical Global Impressions; HARS = Hamilton Anxiety Rating Scale; MADRS = Montgomery-Asberg Depression Rating Scale; PANSS = Positive and Negative Syndrome Scale; PSQI = Pittsburgh Sleep Quality Index; PTSD = posttraumatic stress disorder; SF-36 V MCS = Veterans RAND 36-item Health Survey, mental component score; SF-36 V PCS = Veterans RAND 36-item Health Survey, physical component score; VA = US Department of Veterans Affairs; WWI = World War I; WWII = World War II.

items that are rated from 0 (very dissatisfied) to 7 (very satisfied) that assess contentment with one's living situation, relationships, work, safety, and well-being.

Data Analysis

Data analyses proceeded in 4 phases. First, baseline demographic, military, and clinical characteristics of patients randomized to placebo versus risperidone were compared by using independent-sample *t* tests for continuous variables and Fisher tests for categorical variables. Second, to evaluate the relation between overall sleep quality (total PSQI scores) at baseline and PTSD symptom severity and measures of functioning (CAPS, SF-36 V MCS, SF-36 V PCS, and BLSI scores), we conducted multivariable linear regression analyses with theoretically relevant demographic, trauma, and clinical variables entered as covariates. If significant effects of total PSQI scores were observed, post hoc analyses were conducted to evaluate associations among subscales of the PSQI and dependent measures; α was set to .01 in these analyses to reduce the likelihood of type 1 error. Third, to evaluate the effect of risperidone treatment on total PSQI scores, we conducted a series of linear mixed-effects models. Treatment, time, and the treatment × time interaction were entered as fixed effects; baseline scores[50] as a fixed covariate, site and patient as random effects; and PSQI total and subscale scores and CAPS sleep-related items as dependent variables in separate analyses. Fourth, we conducted bivariate correlations of slopes in the risperidone condition to evaluate how changes in PSQI total scores related to changes in CAPS, SF-36 V MCS, SF-36 V PCS, and BLSI scores.

RESULTS

Demographics

Table 1 shows baseline demographic and military characteristics of the sample. 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 participation in combat (n = 209, 78.3%).

Nature and Clinical Impact of Sleep Disturbance

Table 2 shows mean total and subscale PSQI scores at baseline. Mean total PSQI scores were elevated, with 235 veterans (88.0%) scoring > 5,

Table 2. Mean Pittsburgh Sleep Quality Index (PSQI) Total and Subscale Scores at Baseline in the Full Sample and Bivariate Correlations With Measures of PTSD Symptoms, Functioning, and Life Satisfaction

			Bivariate Correlations							
			CAPS		SF-36 V PCS		SF-36 V MCS		BLSI	
Measure	Mean (SD)	Range	*r*	*P*	*r*	*P*	*r*	*P*	*r*	*P*
PSQI, total score	13.68 (3.87)	3–21	0.29	<.001	−0.32	<.001	−0.22	.001	−0.23	<.001
Sleep quality	2.10 (0.80)	0–3	0.42	<.001	−0.26	<.001	−0.31	<.001	−0.30	<.001
Sleep latency	2.12 (0.98)	0–3	0.18	.003	−0.18	.005	−0.07	.25	−0.20	.002
Duration of sleep	1.80 (1.14)	0–3	0.25	<.001	−0.30	<.001	−0.07	.24	−0.25	<.001
Sleep efficiency	1.49 (1.26)	0–3	0.02	.70	−0.11	.071	0.06	.33	0.05	.42
Sleep disturbance	2.16 (0.64)	1–3	0.21	.001	−0.31	<.001	−0.14	.029	−0.11	.10
Need medication to sleep	1.98 (1.33)	0–3	0.21	.001	−0.31	<.001	−0.14	.029	−0.11	.10
Daytime dysfunction	1.96 (0.80)	0–3	0.28	<.001	−0.12	.057	−0.33	<.001	−0.32	<.001

Abbreviations: BLSI = Boston Life Satisfaction Inventory; CAPS = Clinician-Administered PTSD Scale; PTSD = posttraumatic stress disorder; SF-36 V MCS = Veterans RAND 36-item Health Survey, mental component score; SF-36 V PCS = Veterans RAND 36-item Health Survey, physical component score.

Table 3. Results of Multivariable Linear Regression Analyses of Factors Associated With Measures of PTSD Symptom Severity, Mental and Physical Health-Related Quality of Life, and Life Satisfaction

	Total CAPS (R^2 = 0.13)		SF-36 V PCS (R^2 = 0.24)		SF-36 V MCS (R^2 = 0.28)		BLSI (R^2 = 0.33)	
	β	*P*	β	*P*	β	*P*	β	*P*
Age	−0.17	.017	0.03	.65	0.03	.64	0.26	<.001
Male sex	0.07	.31	0.05	.44	−0.02	.77	0.02	.78
Nonwhite race/ethnicity	0.02	.79	−0.21	.002	0.15	.013	−0.07	.23
Education (years)	0.02	.77	0.04	.48	−0.11	.063	−0.03	.58
Combat exposure severity	0.11	.12	−0.04	.60	0.08	.17	−0.02	.76
CTQ total score	0.00	.96	0.12	.052	0.02	.73	−0.03	.56
Number of medical conditions	0.02	.73	−0.25	<.001	0.02	.73	−0.01	.94
Alcohol use disorder (past month)	−0.01	.87	0.09	.14	0.01	.93	−0.04	.47
Cannabis use disorder (past month)	−0.04	.52	0.01	.90	0.07	.20	−0.03	.57
No. of cigarettes/d	−0.01	.90	0.06	.37	0.01	.85	0.02	.77
No. of caffeinated drinks	0.03	.63	−0.04	.54	0.03	.64	0.04	.54
CAPS total score	…	…	−0.09	.25	−0.24	<.001	−0.32	<.001
MADRS total score[a]	…	…	−0.07	.33	−0.45	<.001	−0.23	.001
PSQI total score	0.29	<.001	−0.24	<.001	0.01	.94	−0.04	.53

[a]MADRS scores were excluded from analyses predicting total CAPS scores because of the high correlation between MADRS and CAPS scores (r = 0.49, P < .001).

Abbreviations: BLSI = Boston Life Satisfaction Inventory; CAPS = Clinician-Administered PTSD Scale; CTQ = Childhood Trauma Questionnaire; MADRS = Montgomery-Asberg Depression Rating Scale; PSQI = Pittsburgh Sleep Quality Index; PTSD = posttraumatic stress disorder; SF-36 V MCS = Veterans RAND 36-item Health Survey, mental component score; SF-36 V PCS = Veterans RAND 36-item Health Survey, physical component score.

which is indicative of clinically significantly impaired sleep. Domains of sleep in which the most pronounced sleep difficulties were evident were sleep disturbance, sleep latency, and sleep quality.

Table 3 shows results of multivariable linear regression analyses evaluating correlates of total CAPS, SF-36 V PCS, SF-36 V MCS, and BLSI scores. After adjustment for demographic, trauma, and clinical variables, total PSQI scores were associated positively with total CAPS scores and negatively with SF-36 V PCS scores. Post hoc analyses revealed that scores on the sleep quality subscale of the PSQI were independently positively associated with total CAPS scores (β = 0.35, t = 5.38, P < .001) and that scores on the sleep disturbance subscale of the PSQI were independently negatively associated with SF-36 V PCS scores (β = −0.22, t = 3.17, P = .002); none of the other PSQI subscales were significant in these analyses (all β values < 0.15, all t tests < 2.32, all P values > .02). Post hoc analyses of SF-36 V PCS subscales revealed that total PSQI scores were negatively associated with bodily pain (β = −0.26, t = 3.98, P < .001) and physical functioning (β = −0.23, t = 3.32, P = .001), but not general health (β = −0.10, t = 1.42, P = .16) or role-physical functioning (β = −0.13, t = 1.94, P = .054) scores.

Effects of Risperidone Treatment

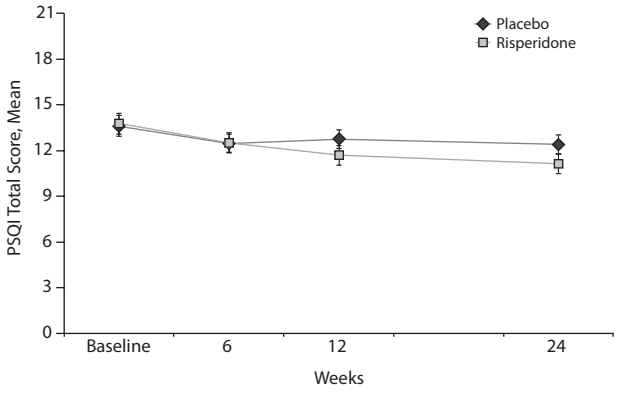
Table 4 shows results of linear mixed-effects models evaluating the effect of risperidone treatment on PSQI total scores. Analyses revealed significant effects of treatment ($F_{1,228}$ = 4.57, P = .034) and treatment × time ($F_{2,421}$ = 4.32, P = .014) on total PSQI scores. Significant effects relative to placebo emerged at 24 weeks (Figure 1), but these effects were no longer significant after adjustment was made for the effects of sleep medications not related to the study. The treatment-by-time interaction was also significant for the use of sleep medication subscale. As shown in Table 4, statistically significant main effects of treatment, which were modest in magnitude, were observed for total PSQI scores and duration of sleep and sleep quality subscales,

Table 4. Results of Linear Mixed-Effects Models Evaluating Effect of Risperidone Versus Placebo Treatment on PSQI and CAPS Sleep Measures

	Treatment		Time		Treatment × Time	
Variable	*F*	*P*	*F*	*P*	*F*	*P*
Total PSQI score	4.57	.034	4.62	.010	4.32	.014
Sleep quality	3.86	.050	6.75	.001	2.48	.085
Sleep latency	1.00	.32	0.67	.51	1.61	.20
Duration of sleep	15.08	<.001	3.84	.022	2.71	.068
Sleep efficiency	1.63	.20	1.08	.34	1.02	.36
Sleep disturbance	2.95	.087	1.80	.17	1.17	.31
Need medication to sleep	0.90	.34	0.48	.62	3.59	.028
Daytime dysfunction	0.97	.33	3.68	.026	1.04	.35
CAPS						
Nightmares	4.60	.033	2.39	.092	1.51	.22
Sleep difficulties	2.50	.11	1.18	.31	3.90	.021
Mean scores and effect sizes for significant main effects of risperidone treatment						
	Placebo, Mean (SD)		Risperidone, Mean (SD)		Cohen *d* (95% CI)	
Total PSQI score	12.55 (0.25)		11.77 (0.26)		0.26 (0.02–0.50)	
Duration of sleep	1.63 (0.06)		1.28 (0.06)		0.48 (0.23–0.72)	
Sleep quality	1.86 (0.05)		1.71 (0.05)		0.24 (0.01–0.48)	
CAPS item						
Nightmares	3.91 (0.15)		3.43 (0.15)		0.26 (0.02–0.50)	

Abbreviations: CAPS = Clinician-Administered PTSD Scale; PSQI = Pittsburgh Sleep Quality Index.

Figure 1. Total Pittsburgh Sleep Quality Index (PSQI) Scores in Placebo and Risperidone Conditions Over 24-Week Study Period[a]



[a]Error bars represent 95% CIs. Analyses revealed significant effects of treatment ($F_{1,228}$ = 4.57, P = .034) and treatment-by-time ($F_{2,421}$ = 4.32, P = .014) on total PSQI scores. Mean values differed significantly at 24-week follow-up assessment (P = .0055). However, this difference was not significant after adjustment was made for the impact of sleep medications not related to the study.

with the risperidone group scoring lower than the placebo group on these measures. Linear mixed-effects models of sleep items from the CAPS revealed a significant main effect of risperidone treatment on recurring and distressing nightmares of military-related traumatic events (main effect of drug: $F_{1,248}$ = 4.60, P = .033), as well as a significant effect of treatment × time on sleep difficulties.

Analyses of change scores in the risperidone condition revealed that greater reductions in PSQI scores over the 24-week study period were associated with greater reductions in total CAPS (r = −0.28, P = .001) and greater improvement in SF-36 V MCS (r = 0.26, P = .003) scores; correlations of change scores for PSQI and SF-36 V PCS (r = −0.02, P = .80) and BLSI (r = −0.02, P = .85) scores were not significant.

DISCUSSION

The current report from a large multicenter VA clinical trial reveals two principal sets of findings related to sleep impairment in PTSD. First, the data make a strong case that sleep is very disrupted in patients with chronic military-related PTSD who have not responded well to antidepressant treatment. A remarkable 88% of the veterans with PTSD in this study manifested clinically significant sleep impairment, defined as a score of greater than 5 on the PSQI, a widely used sleep outcome measure. This rate is double the rate of insomnia in US military personnel recently returned from Iraq and Afghanistan[8] and nearly 4 times the rate of insomnia associated with PTSD in Veterans Health Administration service users, nationally.[51] In this study, sleep impairment was associated with more severe PTSD and poorer quality of life as assessed by several scales of psychosocial and medical well-being (SF-36 V PCS, SF-36 V MCS, BLSI). Thus, the current study provides compelling evidence that PTSD patients who do not respond adequately to antidepressant treatments may constitute a population with a particularly urgent need for further behavioral or pharmacologic treatments for insomnia.

Second, the current data suggest that adjunctive risperidone has a profile of clinical efficacy for insomnia associated with PTSD that is both modest and delayed. Risperidone had a small effect on sleep overall (PSQI total score, d = 0.24), a small and marginally significant effect on sleep quality (PSQI sleep quality subscale, d = 0.24) and nightmares (CAPS nightmare item, d = 0.26), and a moderate effect on increasing sleep duration (PSQI sleep duration subscale, d = 0.48). However, the temporal profile of risperidone's effects upon sleep was quite striking in that risperidone effects did not significantly differ from placebo until week 24. This delay in efficacy for the treatment of insomnia must be considered a significant limitation in the efficacy of risperidone. This delay in the onset of efficacy also suggests that risperidone's effects on sleep are different from the typical hypnotic medication, exemplified by benzodiazepines, which produce maximal benefit rapidly. These late-appearing effects did not arise from differential attrition, as attrition rates were low and did not significantly differ across groups (approximately 15% in each group).

The beneficial effects of risperidone upon sleep were clinically significant in that they were correlated with reductions in PTSD symptom severity (CAPS total score) and improvement in the SF-36 V MCS. These positive clinical results contrast with risperidone effects on the CAPS. In the initial report[39] from this study, risperidone produced small

but statistically significant reductions in the hyperarousal and reexperiencing subscale scores on the CAPS. However, these effects, which were significant statistically, were not deemed to be clinically meaningful, as they were not correlated with global clinical or quality of life outcome measures. Thus, the current result might be interpreted to suggest that risperidone effects on sleep disturbance are more clinically meaningful than risperidone's effects on core PTSD symptoms. However, the failure of risperidone improvements in sleep to be associated with global clinical status (Clinical Global Impressions), physical quality of life, and other general measures of quality of life (BLSI) suggests that effects of risperidone on sleep have limited clinical significance.

The findings of the current study may have broad implications for the treatment of PTSD, as this is the largest study to date of a second-generation antipsychotic for the treatment of PTSD and the first multicenter study evaluating a pharmacologic strategy for antidepressant-resistant symptoms for military-related PTSD.[39] However, limitations of this study should be noted. First, the majority of patients in this study were treated with more than 1 psychotropic medication (mean [SD] medications per patient: risperidone, 3.09 [1.69]; placebo, 2.86 [1.46]), including a subgroup of patients on medication known to influence sleep (mirtazapine, trazodone, nefazodone, quetiapine). The presence of these medications may have reduced the magnitude of the benefit produced by risperidone in the current study. Second, the patients enrolled in this study had a high frequency of comorbid psychiatric disorders, including smoking and alcohol abuse, which may have influenced their clinical course. Lastly, we studied predominately men with chronic military-related PTSD who also failed to respond to antidepressants. It is possible that females, patients with less severe or chronic PTSD, or those who had a more favorable pattern of antidepressant response might have responded more favorably to risperidone.

In summary, this study makes a strong case for the clinical significance of sleep impairments in chronic military-related PTSD and a rather weak case for treating these symptoms with risperidone. Overall, there was a very high rate of severe sleep disturbances in this large sample of veterans with chronic military-related PTSD who had a history of inadequate treatment response to serotonergic antidepressant medications. In this population, sleep disturbance was correlated with more severe PTSD, functional impairment, and poorer mental health–related quality of life and worse physical quality of life. Risperidone significantly improved some aspects of sleep, such as sleep duration and nightmares. However, statistically significant benefits of risperidone did not emerge until 24 weeks of treatment in the initial analysis, although this observation did not persist after adjusting for differential utilization of nonstudy sleep medications (trazodone, nefazodone, mirtazapine, quetiapine). Thus, the modest improvement in sleep produced by risperidone was associated with reductions in PTSD symptoms and a limited spectrum of improvement in quality of life. In light of these findings, the identification of safe and effective strategies for treating sleep disturbances associated with PTSD remains a high-priority research objective.

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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-Davino, 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. Teppen, J. Yount (Chicago, Illinois); E. Konicki, V. Nero, E. Smith, R. Slepecky (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. Logan, 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, New Mexico). *Data Monitoring Committee*: T. Grieger (Falls Church, Virginia), D. Blake (Boise, Idaho), K. Dickerson (Baltimore, Maryland), M. Thase (Philadelphia, Pennsylvania), P. Harvey (Miami, Florida). *Executive Committee*: K. Jones (Perry Point, Maryland), J. Vertrees (Albuquerque, New Mexico), M. Stein (San Diego, California), C. Stock (Salt Lake City, Utah), M. Hertzberg (Durham, North Carolina), E. Duncan (Atlanta, Georgia), J. Gelernter (New Haven, Connecticut). *Planning Committee*: D. Ciraulo, D. Kaloupek (Boston, Massachusetts); M. Stein (San Diego, California); G. Bartzokis (Los Angeles, California); A. Rasmusson (West Haven, Connecticut); J. Davidson (Durham, North Carolina); C. Marmar (San Francisco, California); P. Lavori (Menlo Park, California); S. Berkowitz, T. O'Leary, B. Schuster (Washington, DC); K. Jones, J. Collins, C. Howell (Perry Point, Maryland); J. Vertrees (Albuquerque, New Mexico); D. Bradham (Baltimore, Maryland); M. Friedman (White River Junction, Vermont).

Potential conflicts of interest: During the planning, conduct, data analysis, and publication of the main paper from Veterans Affairs (VA) Cooperative Study #504, **Dr J Krystal** had no personal financial relationship with Johnson & Johnson; however, subsequent to that publication, Johnson & Johnson licensed a patent related to the use of ketamine as an antidepressant in which he was a co-sponsor. He is a co-sponsor for a patent related to the use of riluzole for psychiatric disorders, which has been licensed by Biohaven Medical Sciences, and is a shareholder in that company. He is a co-sponsor for the patent related to dopamine and noradrenergic reuptake inhibitors in the treatment of schizophrenia and has served as a scientific consultant with compensation of less than $10,000 per year to AbbVie, AMGEN, Astellas Pharma Global Development, AstraZeneca, Biomedisyn, Bristol-Myers Squibb, Eli Lilly, Euthymics Bioscience, Neurovance (a subsidiary of Euthymic Bioscience), Janssen Research & Development, Lundbeck Research, Novartis Pharma AG, Otsuka America, Sage Therapeutics, Sunovion, and Takeda; served on the scientific advisory board for Lohocla Research, Mnemosyne, Naurex, and Pfizer; holds stock in Mnemosyne; and is Editor for *Biological Psychiatry*. **Dr A Krystal** received grant/research

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