Placebo-Controlled Trial of Risperidone Augmentation for Selective Serotonin Reuptake Inhibitor–Resistant Civilian Posttraumatic Stress Disorder

Barbara O. Rothbaum, Ph.D.; Therese K. Killeen, Ph.D.; Jonathan R. T. Davidson, M.D.; Kathleen T. Brady, M.D., Ph.D.; Kathryn M. Connor, M.D., M.H.S.; and Mary H. Heekin, M.S.W.

Objective: Treatment of posttraumatic stress disorder (PTSD) with pharmacotherapy is promising, although the response to medication has generally been modest, and strategies to improve the response to antidepressant medications are needed. The primary objective of this study was to examine risperidone augmentation in civilians with PTSD currently receiving sertraline without an optimal response.

Method: Male and female participants aged 18 to 65 years were recruited from 3 academic medical centers between June 2004 and September 2006. Those who met eligibility criteria with a DSM-IV diagnosis of PTSD subsequent to a civilian trauma and a Clinician-Administered PTSD Scale (CAPS) score greater than or equal to 50 at screen and baseline were entered into phase 1. In phase 1, patients were treated for 8 weeks with open-label sertraline. Those who did not remit (defined as a 70% decrease in PTSD symptoms as measured by the CAPS) were entered into phase 2. In phase 2, patients remained on sertraline and were randomly assigned to augmentation with risperidone or matching pill placebo for 8 weeks. Symptoms of PTSD and depression and psychotic symptoms were measured prospectively throughout the 16-week study.

Results: Of the 45 patients enrolled, 34 completed phase 1, and 25 of those patients were randomly assigned to phase 2; 20 completed phase 2. For all patients across all phases, PTSD and related symptoms improved with no significant differences between groups. In post hoc analyses, the group that received risperidone augmentation had significantly more improvement than the placebo group on the Davidson Trauma Scale (DTS) sleep item ($p = .03$) and demonstrated a trend toward significantly more improvement on the Clinical Global Impressions-Improvement scale ($p = .066$), the positive ($p = .065$) and paranoia ($p = .1$) subscales of the Positive and Negative Syndrome Scale, and the CAPS sleep item ($p = .09$).

Conclusion: Participants responded well to sertraline in phase 1, sustained their response, and displayed a placebo response comparable with that of risperidone in phase 2. There is some evidence to support the conclusion that risperidone augmentation was helpful in those subjects who did not remit with sertraline alone, particularly in the areas of global improvement, positive affect, and sleep.

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Received April 25, 2007; accepted July 30, 2007. *From the Department of Psychiatry, Emory University School of Medicine, Atlanta, Ga. (Dr. Rothbaum and Ms. Heekin); Clinical Neuroscience Division, Department of Psychiatry, Medical University of South Carolina, Charleston (Drs. Killeen and Brady); and Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine, Durham, N.C. (Drs. Davidson and Connor).*

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Corresponding author and reprints: Barbara O. Rothbaum, Ph.D., Department of Psychiatry, Emory University School of Medicine, 1841 Clifton Rd., NE, Atlanta, GA 30329 (e-mail: brothba@emory.edu).

The prevalence of posttraumatic stress disorder (PTSD) has been estimated to be 9%[1] to 12.3% in the general population,[2] clearly indicating that the disorder is a major public health concern. Symptom clusters of PTSD include reexperiencing of the traumatic event, avoidance of reminders with narrowing of affect, and hyperarousal and are associated with functional impairment and social and financial impact.[3] Sertraline and paroxetine, both selective serotonin reuptake inhibitors (SSRIs), have received U.S. Food and Drug Administration (FDA) approval for the treatment of PTSD[4–6]; however, the response to medication has generally been modest. In the trials of these SSRIs submitted for FDA approval, 42% of participants treated with paroxetine failed to meet criteria for a responder,[6] and 47% of participants treated with sertraline failed to meet response criteria in 1 trial[4] and 40% failed in another.[5] Therefore, strategies to bolster the response to antidepressant medications are warranted. Evidence is accumulating to suggest that atypical antipsychotics are an effective adjunct

to treatment with SSRIs in treatment-resistant depression and in combat veterans with PTSD.[7] A recent review of data supports augmentation treatment for refractory unipolar and bipolar depression as well as anxiety disorders.[8]

Open trials in patients with combat-related PTSD have indicated that the atypical antipsychotic quetiapine is effective as a monotherapy or as an augmentation strategy. Quetiapine was effective in an 8-week study of veterans diagnosed with PTSD with psychotic features resistant to prior pharmacotherapy with antidepressants.[9] Hamner et al.[10] reported success with quetiapine in reducing PTSD reexperiencing symptoms in addition to positive and negative psychotic symptoms and depressive symptoms. Stein et al.[11] demonstrated improvement in PTSD symptoms using olanzapine as adjunctive therapy. Specific benefits were noted both within sleep measures and measures rating depressive symptoms. In their 2005 review, Hamner and Robert[12] identified multiple compelling arguments for continued research into the efficacy of atypical antipsychotic medications to treat resistant PTSD as well as PTSD with complex comorbid diagnosis. Rationale for atypical antipsychotic treatment includes a biological basis for treatment and reported success in treating various comorbid symptoms that are often included in a PTSD diagnosis. Adjunctive use of risperidone reduced irritability in individuals with combat-related PTSD.[13] Other studies utilizing risperidone as monotherapy or augmentive treatment also report favorable results in this veteran population.[14,15] Reich et al.[16] found preliminary evidence for the positive and safe use of this atypical antipsychotic in treatment of PTSD in women with a history of childhood abuse. However, risperidone has yet to be tested as an adjunct to antidepressant treatment in a double-blind placebo-controlled trial in civilians with PTSD. The primary objective of the present study was to compare the response of civilians with PTSD currently receiving sertraline without an optimal response randomly assigned to receive either risperidone augmentation or matching placebo.

METHOD

Research participants gave their informed consent after the procedures and possible side effects were fully explained. Institutional review board approval was obtained for the investigation from each participating institution. Male and female participants aged 18 to 65 years were recruited from 3 academic medical centers (Emory University School of Medicine, Atlanta, Ga.; Medical University of South Carolina, Charleston; and Duke University School of Medicine, Durham, N.C.) between June 2004 and September 2006. Participants were recruited from radio, newspaper and Internet ads, flyers distributed to clinicians and posted in public places in the community, and clinical programs. Those who met eligibility criteria with a DSM-IV diagnosis of PTSD subsequent to a civilian trauma and a Clinician-Administered PTSD Scale[17] (CAPS) score of greater than or equal to 50 at screen and baseline were entered into phase 1 of the study (sertraline only). Trauma history was obtained with the Life Events Checklist,[18] which was administered at screening and consists of a list of 17 trauma- and stress-related events. Participants who endorsed any event that was combat related were excluded if this was the event that was causing the most distress or generating the PTSD symptoms. The nature of the civilian trauma included sexual abuse (7 participants), physical abuse (3 participants), accident (4 participants), domestic violence (2 participants), a witnessed killing (1 participant), a break-in (1 participant), a witnessed suicide attempt (1 participant), and stalking (1 participant). Comorbidity was determined by use of the Mini-International Neuropsychiatric Interview for DSM-IV, version 5.0.[19]

During phase 1, participants were treated with open-label sertraline for 8 weeks starting at 25 mg/day, then increased to 50 mg/day, and then given in 50-mg increments to a maximum dose of 200 mg/day. The clinical titration of sertraline was completed by week 4 to allow 4 weeks on the maximum dose. Participants were assessed at baseline and weeks 1, 2, 4, 6, and 8. If a 70% decrease in PTSD symptoms (CAPS) was not achieved by week 8, the individual was entered into phase 2 (augmentation) of the study.

During phase 2, individuals maintained their current dose of sertraline, which was augmented by either risperidone or matching pill placebo administered in a double-blind fashion. Risperidone was initially dosed at 0.5 mg/day, and then increased with weekly titration by 0.5 mg/day as tolerated up to a maximum daily dose of 2 mg, although up to 3 mg was permissible on a case-by-case basis. In this way, all subjects who completed phase 2 achieved steady state after 3 to 4 weeks and spent another 4 weeks on a stable dose. Participants were assessed at weeks 8, 9, 10, 12, 14, and 16. Measures included the CAPS, Davidson Trauma Scale[20] (DTS), Positive and Negative Syndrome Scale[21] (PANSS) for schizophrenia, Beck Depression Inventory[22] (BDI), and Clinical Global Impressions-Improvement scale[23] (CGI-I).

Regarding safety measures, adverse events, concomitant medication vital signs, and weight were monitored on a weekly basis. One participant taking sertraline 100 mg experienced tachycardia after the first week taking risperidone 0.5 mg. At baseline and study completion, complete blood count and blood chemistry including levels of liver enzymes, electrolytes, glucose, bilirubin, and total protein were assessed. Only 1 participant who was taking sertraline 200 mg and risperidone 1.0 mg had elevated liver enzyme levels. Hemoglobin A1c levels were assessed at baseline, at randomization, and at study completion. Waist circumference and body mass index

Table 1. Baseline Demographic Characteristics of 20 Civilian Patients With PTSD Who Completed Phase 2[a]

Characteristic	Risperidone (N = 9)	Placebo (N = 11)
Age, mean ± SD	33.4 ± 10.7	34.8 ± 11.9
Gender, N (%)		
Female	7 (78)	9 (82)
Male	2 (22)	2 (18)
Race, N (%)		
White	6 (67)	8 (73)
Black	3 (33)	2 (18)
Other	0 (0)	1 (9)
Education, N (%)		
High school/GED	2 (22)	1 (9)
Some college	3 (33)	5 (46)
2-year graduate	2 (22)	1 (9)
4-year graduate	1 (11)	2 (18)
Graduate school	1 (11)	2 (18)
Unemployed, N (%)	2 (22)	3 (27)
Marital status, N (%)		
Single	7 (78)	7 (64)
Married	0 (0)	2 (18)
Divorced	1 (11)	2 (18)
Widowed	1 (11)	0 (0)
Comorbid diagnoses, N (%)		
Major depressive disorder	8 (89)	8 (73)
Low/medium suicide risk	4 (44)	4 (36)
Any other anxiety disorder	5 (56)	6 (55)
Panic	2 (22)	3 (27)
Social phobia	3 (33)	3 (27)
Generalized anxiety disorder	2 (22)	3 (27)

[a]Not significant.
Abbreviations: GED = general equivalency diploma, PTSD = posttraumatic stress disorder.

Table 2. Total CAPS Score (frequency plus intensity) Across Time for Civilian Patients With PTSD Randomly Assigned to Risperidone or Placebo[a]

Total CAPS Score	N	Mean	SD	Mean SE
Baseline				
Placebo	11	76.2727	13.27472	4.00248
Risperidone	14	76.3571	15.29508	4.08778
Week 8				
Placebo	11	60.0000	21.45227	6.46810
Risperidone	14	56.0000	20.91006	5.58845
Week 16				
Placebo	11	36.4545	21.03979	6.34374
Risperidone	9	38.8889	24.43586	8.14529

[a]Not significant (F = 0.078, p = .8).
Abbreviations: CAPS = Clinician-Administered PTSD Scale, PTSD = posttraumatic stress disorder.

Table 3. Clinical Global Improvement Across Time Postrandomization for Civilian Patients With PTSD[a]

CGI Score	N	Mean	SD	Mean SE
Week 8				
Placebo	11	3.18	1.168	0.352
Risperidone	14	3.00	1.109	0.296
Week 12				
Placebo	11	2.45	0.820	0.247
Risperidone	9	2.78	1.093	0.364
Week 16				
Placebo	11	2.27	1.009	0.304
Risperidone	9	2.00	0.866	0.289

[a]General linear model repeated-measures analysis of variance with postrandomization scores as covariate; trend for time-by-group interaction from week 12 to week 16 (F = 3.87, p = .066).
Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, PTSD = posttraumatic stress disorder.

were measured at baseline and study completion. At baseline, randomization, and study completion, participants were administered the Abnormal Involuntary Movement Scale,[24] Barnes Akathisia Scale,[25] and Simpson-Angus Scale.[26] The scores for these scales remained unchanged throughout the study with no significant differences between groups.

Baseline demographic characteristics were analyzed with independent t tests for continuous data and χ^2 analysis for categorical data. The outcome measures of the CAPS total score with cluster subscales and sleep (severity and frequency combined) and nightmare items, CGI-I score, DTS total score and sleep combined severity and frequency items, BDI total score, and PANSS subscale scores were analyzed using a 2-way repeated-measures analysis of variance with time and group assignment as fixed factors taken from the point of randomization.

RESULTS

Ninety-one patients consented to treatment and were screened; 50 of those patients completed baseline assessment, of whom 45 were eligible to enter phase 1. Thirty-four patients completed phase 1; 25 of those patients were randomly assigned to phase 2, and 20 completed phase 2 (risperidone: N = 9, placebo: N = 11). Results are reported for those who completed phase 2; demographic characteristics for these patients are presented in Table 1. The mean dose of sertraline at endpoint was 164 mg overall, and the mean dose of risperidone and placebo was 1.9 mg (2.1 mg for those taking risperidone, and 1.7 mg for those taking placebo dosed as risperidone). The mean dose of sertraline at endpoint for those taking risperidone was 147 mg versus 177 mg for those taking placebo. The difference in the sertraline doses between groups was not significant. Regarding participants who reached the 200-mg dose of sertraline, 5 (56%) of 9 were taking risperidone and 8 (73%) of 11 were taking placebo. Means and standard deviations for the major measures are presented in Tables 2 through 5.

Posttraumatic stress disorder and related symptoms improved significantly over time for all participants regardless of treatment condition, with no significant differences between groups (F = 0.078, p = .8). The CAPS scores decreased a mean (SD) of 28.5 (26.6) points from baseline to the end of phase 1 and decreased from randomization to endpoint a further 23.1 (12.9) points for those receiving risperidone and 23.5 (19.6) points for those receiving placebo. Because we had a small sample

Table 4. Beck Depression Inventory (BDI) Scores Across Time for Civilian Patients With PTSD Randomly Assigned to Risperidone or Placebo[a]

BDI Score	N	Mean	SD	Mean SE
Baseline				
Placebo	11	23.1	11.2	3.4
Risperidone	14	25.4	10.5	2.8
Week 8				
Placebo	11	20.4	13.5	4.1
Risperidone	14	13.1	14.0	3.7
Week 16[b]				
Placebo	11	13.6	9.1	2.7
Risperidone	14	13.2	9.3	2.5

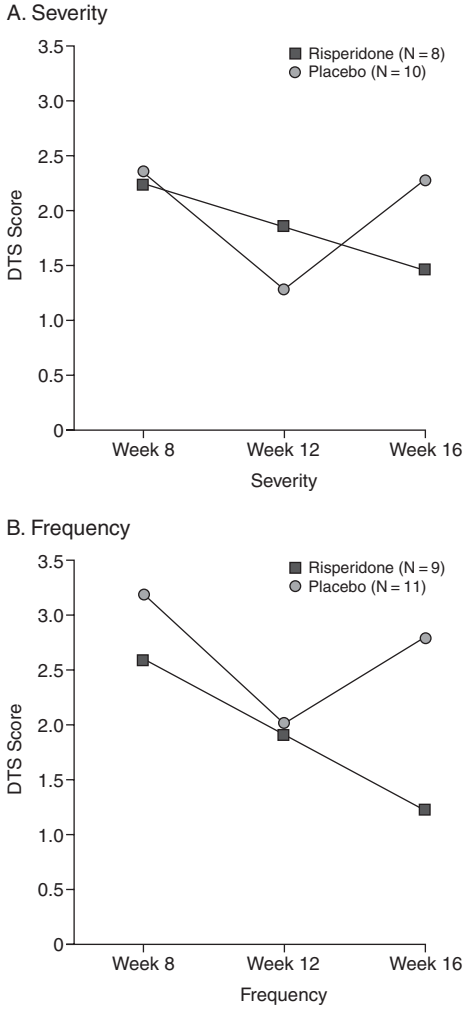
[a]Not significant (F = 0.874, p = .37).
[b]Last observation carrried foward.
Abbreviation: PTSD = posttraumatic stress disorder.

Table 5. Davidson Trauma Scale (DTS) Scores Across Time for Civilian Patients With PTSD Randomly Assigned to Risperidone or Placebo[a]

DTS Score	N	Mean	SD	Mean SE
Baseline				
Placebo	11	71.0	15.0	4.5
Risperidone	14	75.0	24.3	6.5
Week 8				
Placebo	11	59.9	25.7	7.8
Risperidone	14	49.4	30.0	8.0
Week 16[b]				
Placebo	11	37.3	26.1	7.9
Risperidone	14	33.5	27.8	7.4

[a]Not significant (F = 0.001, p = .97).
[b]Last observation carrried foward.
Abbreviation: PTSD = posttraumatic stress disorder.

Figure 1. Davidson Trauma Scale (DTS) Sleep Severity and Frequency Item Scores for Civilian Patients With PTSD[a,b]



[a]F = 5.564, p = .03.
[b]Last observation carrried foward.
Abbreviation: PTSD = posttraumatic stress disorder.

and all participants were already taking active medication (i.e., sertraline), we also examined statistical trends for items or subscales of interest that were not statistically significant at the conventional levels of significance in post hoc analyses. There were group-by-time interaction trends for the CAPS sleep difficulty item across time: general linear model repeated measures for visits 10 (week 12) and 12 (week 16) with visit 7 (week 8/randomization visit) as covariate (F = 3.2, p = .09) favoring greater improvement for the risperidone versus placebo groups.

The DTS was administered on a weekly basis throughout the intervention, and at least 1 post-randomization outcome was collected on the 25 randomly assigned participants. Using a last-observation carried-forward procedure for the 25 randomly assigned participants on the DTS sleep combined frequency and severity item, there was a significant group-by-time interaction from visit 10 (12 weeks) to visit 12 (16 weeks) (F = 5.564, p = .03) such that the group that received risperidone augmentation had significantly more improvement than the placebo group (Figure 1A and B), although there were no differences on the nightmare item. There was a trend for the group that received risperidone augmentation to have greater improvement from visit 10 (week 12) to visit 12 (week 16) as compared with the placebo group on the CGI-I (F = 3.87, p = .066).

On the PANSS, there were trends toward significantly more improvement on the positive subscale, which measures delusions, conceptual disorganization, hallucinatory behavior, excitement, grandiosity, suspiciousness/persecution, and hostility (general linear model repeated measures with baseline [visit 2] as covariate [time × group interaction] from visit 7 [randomization visit] to visit 12 [F = 3.899, p = .065]), and on the paranoia subscale (p = .1) between visit 7 (8 weeks) and visit 12 (16 weeks) with baseline as covariate. There were no other between-group differences on any of the other PANSS subscale scores.

The 5 study participants who discontinued early from phase 2 were all taking risperidone; 4 were withdrawn

due to adverse events that were possibly study related. These participants, who were withdrawn because of adverse events, included (1) a 26-year-old white man with tachycardia (rate of 120 bpm) 1 week postrandomization who was taking risperidone 0.5 mg and sertraline 100 mg; (2) a 43-year-old white man taking risperidone 1.0 mg and sertraline 200 mg removed from the study 2 weeks post-randomization with elevated liver enzyme levels (aspartate aminotransferase, alanine aminotransferase, and γ-glutamyltransferase); (3) a 35-year-old white woman who weighed 267 lb and was a heavy smoker taking risperidone 0.5 mg and sertraline 150 mg was removed from the study 1 week postrandomization due to visiting the emergency room twice that week with unremitting chest pain; (4) a 28-year-old black woman dropped out after her second week post-randomization taking sertraline 200 mg and risperidone 1.5 mg (she was doing well on the medication but reported not having the time to make her study visit); and (5) a 23-year-old white woman taking sertraline 100 mg who was scheduled to start risperidone 0.5 mg but was withdrawn from the study during the first week post-randomization due to "probable dystonic reaction."

A χ^2 analysis of study termination related to adverse events by treatment group shows a trend for more participants in the risperidone group versus the placebo group terminating the study due to possible study-related adverse events ($\chi^2 = 3.74$, $p = .1$). The only outcome assessments with any post-randomization data for all randomized patients were the DTS and the BDI. As such, the last-observation-carried-forward procedure was used for the 25 randomized participants in the analyses of these measures. There were no between-group differences on either of these 2 measures for total or subscale scores.

CONCLUSION

In general, participants responded well to sertraline in phase 1, sustained their response, and displayed a placebo response comparable with that of risperidone in phase 2. There is some evidence to support the conclusion that risperidone augmentation was helpful in those subjects who did not remit with sertraline alone, particularly in the areas of global improvement, positive affect, and sleep. There were statistically significant differences or trends for more improvement in sleep with risperidone on several of the measures of sleep, indicating a consistent effect on sleep over and above the response from sertraline. There were also trends for improvement on the positive symptoms and paranoia subscales of the PANSS. The fact that all of these patients were taking active medication and received this additional improvement is clinically meaningful, particularly in these areas. Although these participants were not psychotic, many reported symptoms of suspiciousness/persecution and hostility that tend to overlap with the DSM cluster D symptoms of anger and hypervigilance.

Insomnia and distressing dreams or nightmares are both difficult to manage and chronically disabling aspects of the disorder. Consistent with the findings from our study, a recent open-label trial of adjunctive risperidone[27] found that veterans diagnosed with PTSD and resistant to psychopharmacologic intervention treated with risperidone showed improvement not only in overall CAPS scores but also specifically in sleep-related variables measured at 6 weeks. Sleep diaries used in that study were found to be particularly illustrative of change over time.[27] Data collected from a 6-week, open-label trial of quetiapine in a population of combat veterans also provide positive preliminary results for symptoms of sleep disruption, such as quality, latency, and duration.[28] Information gathered from these trials in conjunction with results obtained in this current study of civilians diagnosed with PTSD suggests a powerful argument for continued research in the area of atypical antipsychotic medication as adjunctive therapy for treatment-resistant PTSD and specifically the symptoms of sleep disturbance.

Results were limited by a very small sample size with a lack of power to detect group differences. In addition, as discussed, all patients were taking active medication (sertraline) that has been shown to be effective in treating civilian PTSD before the addition of risperidone or placebo, making it particularly difficult to demonstrate any additional response. To our knowledge, this is the only augmentation trial in PTSD in which the first phase of the study was supervised, as opposed to simply accepting a patient's history that an SSRI was not effective. The possible implications are that our study patients were already on an improvement trajectory with a very different set of expectations and recent experiences with sertraline than if they had already gone through nonstudy protocol treatment. They also had completed 16 weeks of sertraline treatment, and PTSD patients have been shown to report continued improvement over time on longer durations of sertraline, which certainly could have produced a ceiling effect and could account for the lack of group differences.[29] In a recent review of antipsychotic augmentation of SSRIs in obsessive-compulsive disorder, no benefit for augmentation was found unless the SSRI had been administered for at least 12 weeks because of further response to continued SSRI monotherapy.[30] However, the results seem to converge, indicating a possible positive effect on sleep, which is one of the biggest complaints of patients with PTSD and one of the hardest symptoms to impact with conventional treatments. These effects should be explored further in larger samples of patients with PTSD.

Drug names: olanzapine (Zyprexa), paroxetine (Paxil, Pexeva, and others), quetiapine (Seroquel), risperidone (Risperdal), sertraline (Zoloft and others).

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