A Preliminary Study of Risperidone in the Treatment of Posttraumatic Stress Disorder Related to Childhood Abuse in Women

D. Bradford Reich, M.D.; Sherry Winternitz, M.D.; John Hennen, Ph.D.; Tempe Watts, B.A.; and Caroline Stanculescu, B.A.

Background: This study evaluated the effectiveness of risperidone in women for the treatment of posttraumatic stress disorder (PTSD) related to childhood physical, sexual, verbal, and emotional abuse.

Method: Subjects were outpatient adult women, aged 18 to 64 years, with chronic PTSD related to childhood physical, sexual, verbal, or emotional abuse. Data were collected from November 18, 2001, to June 7, 2003. Subjects met DSM-III-R criteria for PTSD and criteria for PTSD on the Clinician-Administered PTSD Scale, 1-month version (CAPS-1). Subjects were randomly assigned to receive risperidone (N = 12) in flexible daily dosages in the range of 0.5 to 8 mg or placebo (N = 9) for 8 weeks. The primary outcome measures were changes in score from baseline on the CAPS-1 and the Clinician-Administered PTSD Scale, 1-week version (CAPS-2).

Results: Risperidone-treated patients had a significantly greater reduction in total score on the CAPS-2 (z=-2.44, p=.015). Risperidone-treated patients also had significantly greater reductions in the intrusive (z=-5.71, p<.001) and hyperarousal (z=-2.74, p=.006) subscale scores of the CAPS-2.

Conclusion: The results of the current study indicate that low-dosage risperidone is a safe and effective treatment for intrusive and hyperarousal symptoms in adult women with chronic PTSD from childhood physical, sexual, verbal, and emotional abuse.

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Received Oct. 22, 2003; accepted June 1, 2004. From the Trauma and Dissociative Disorders Program, McLean Hospital, Belmont (all authors), and the Department of Psychiatry, Harvard Medical School, Boston (Drs. Reich, Winternitz, and Hennen), Mass.

Supported by a research grant from Janssen Pharmaceutica. Corresponding author and reprints: D. Bradford Reich, M.D., McLean Hospital, 115 Mill St., Belmont, MA 02478 (e-mail: reichb@mcleanpo.mclean.org). pidemiologic data indicate that posttraumatic stress disorder (PTSD) has a lifetime prevalence of 1% to 14% in the general population¹ and that it occurs approximately twice as frequently in women as in men.^{2,3} It is associated with considerable psychiatric comorbidity,^{2,4} as well as significant increases in medical costs⁵ and impairment in psychosocial functioning.⁴ Several studies have shown a strong association between childhood abuse and PTSD.^{2,6} In 1 study of adults with documented histories of childhood sexual and physical abuse, 38% of victims of sexual abuse and 33% of victims of physical abuse met DSM-III-R criteria for PTSD.⁶

The sedating properties of atypical antipsychotics, as well as their ability to reduce cognitive and perceptual distortions in psychosis, suggest that these medications may be effective in alleviating symptoms of PTSD. Case reports and open-label studies have indicated that clozapine, olanzapine, and quetiapine may alleviate PTSD symptoms.^{7–12} There have been 2 placebo-controlled studies^{13,14} of olanzapine treatment of military-related PTSD in men. One study¹³ found olanzapine no more effective than placebo, but a second study¹⁴ found adjunctive olanzapine, combined with selective serotonin reuptake inhibitors (SSRIs), to be significantly effective.

One open-label study¹⁵ and 2 placebo-controlled studies^{16,17} have provided evidence that risperidone may be effective in alleviating some core symptoms of combatrelated PTSD in male veterans. An open-label study¹⁵ found risperidone effective in reducing intrusive PTSD symptoms. One placebo-controlled study¹⁶ found risperidone effective in reducing intrusive PTSD symptoms; a second placebo-controlled study¹⁷ showed risperidone effective in alleviating hyperarousal symptoms.

To date, there have been no placebo-controlled studies of atypical antipsychotics in the treatment of non-combat-related PTSD. Our pilot study was designed to assess whether risperidone might be effective in alleviating symptoms of PTSD related to childhood sexual, physical, verbal, and emotional abuse in women.

METHOD

Patient Selection

The study was an 8-week, double-blind comparison of flexible-dosage risperidone 0.5 to 8 mg/day and placebo in female adults with chronic PTSD from childhood physical, sexual, verbal, or emotional abuse. Data were collected from November 18, 2001, to June 7, 2003. Subjects in the study were women aged 18 through 64 years who met DSM-III-R criteria for PTSD according to the Structured Clinical Interview for DSM-III-R (SCID)¹⁸ and the Clinician-Administered PTSD Scale, 1-month version (CAPS-1).19-21 The CAPS is a validated structured interview administered by a trained clinician. It is designed to quantify the frequency and intensity of each of the 17 DSM-III-R-defined PTSD symptoms. The CAPS-1 provides a current and lifetime assessment of these symptoms; the CAPS-2 evaluates these symptoms over a 1-week period and is used to assess changes in symptom severity during treatment.

To be eligible for the study, patients must have had a score of ≥50 on the CAPS-1. All subjects needed to report PTSD related to childhood physical, sexual, emotional, or verbal abuse. All subjects needed to be able to provide informed consent, speak fluent English, and have understanding sufficient to perform all tests and examinations required by the protocol. Exclusion criteria included diagnosis of organic mental disorder or psychotic disorder (schizophrenia, schizoaffective disorder, or mood disorder with psychotic features) in the last 6 months; diagnosis of substance dependence (active within the last 60 days); unstable general medical condition; previous treatment with risperidone for 1 week or more; simultaneous treatment with another antipsychotic or mood stabilizer; enrollment in a drug study within the last 60 days; significant risk of suicide or homicide; entering individual psychotherapy within 3 months of the study; entering group therapy within 1 month of the study; and pregnancy or nursing. Subjects could be taking 1 antidepressant (SSRI, tricyclic, monoamine oxidase inhibitor, bupropion, venlafaxine, mirtazapine, or serotonin antagonist reuptake inhibitor) and/or 1 hypnotic (benzodiazepine, zolpidem, trazodone, nefazodone, or diphenhydramine) at bedtime. The dosages of these medications had to have been constant for 1 month before the study.

The study recruited subjects through newspaper advertisements, flyers, a Web site connected to a local university, and a Web site sponsored by the hospital where the study was conducted (McLean Hospital, Belmont, Mass.). The study was approved by the institutional review board. The benefits and risks of study participation were fully explained to each subject; informed written consent was obtained. Subjects could receive up to \$250 for participating in the study. Subjects treated with pla-

cebo were offered open-label treatment for 8 weeks after completing the study.

Study Design

Subjects were randomly assigned to receive risperidone or placebo for the 8 weeks of the study. Subjects met weekly with either a psychiatrist or clinical nurse practitioner for the 8 weeks of the study. Those receiving risperidone began at a dosage of 0.5 mg q.h.s. and were instructed to increase the dosage to 1 mg/day after 3 days. Risperidone was then increased weekly by up to 1 mg per day per week, as tolerated, to a targeted dosage of 4 mg per day or until subjects reported predominant relief of symptoms. If subjects had not received satisfactory relief of symptoms at targeted dosage by week 5, the dosage could be increased to a maximum of 8 mg per day. Risperidone could be divided into 2 or 3 daily doses. If subjects experienced extrapyramidal effects, they could be treated with benztropine at dosages of up to 2 mg b.i.d. Subjects were instructed to maintain all other psychotropic medications at constant dosages during the study.

At baseline, all subjects were assessed with the Hamilton Rating Scale for Anxiety (HAM-A),²² the Hamilton Rating Scale for Depression (HAM-D),²³ and the Dissociative Experiences Scale (DES).²⁴ They had routine laboratory measures performed, including complete blood cell count, electrolytes, serum urea nitrogen/creatinine levels, liver profile, thyroid screen, pregnancy test, urinalysis, and prolactin level. They were also evaluated using the Abnormal Involuntary Movement Scale (AIMS)²⁵ and Barnes Akathisia Scale.²⁶ At the end of the study, subjects had a repeat prolactin level measured. In addition, they received a repeat AIMS and Barnes Akathisia Scale.

Outcome Measures

The primary outcome measures were the total, intrusive, avoidant, and hyperarousal scores on the CAPS-1 and CAPS-2. At baseline, subjects were evaluated using the CAPS-1 and CAPS-2. Subjects were subsequently administered the CAPS-2 at weeks 1, 2, 4, and 8. The CAPS-1 was readministered at week 8. In addition, at week 8, subjects received a repeat physical examination. Subjects discontinuing the study early were evaluated, if possible, with the same assessment they would have received at week 8. Observed or reported adverse experiences were recorded with respect to time of onset, severity, action taken, and outcome.

Statistical Methods

Subject characteristics and baseline measures were compared between active drug and placebo subgroups using χ^2 and t tests. Placebo and active drug subgroups were contrasted on mean change in score from baseline on the CAPS-1 and CAPS-2 using random-effects time series modeling methods (feasible generalized least

Table 1. Baseline Demographic and Clinical Characteristics of Adult Female Subjects With PTSD Related to Childhood Abuse

	Risperidone	Placebo	Fisher Exact	
Characteristic	(N = 12)	(N = 9)	or $t (df = 19)$	p Value
Age, mean (range), y	30.6 (18-56)	24.2 (19–34)	0.67	.42
Race, N (%)				
Caucasian	9 (75.0)	9 (100.0)	2.63	.23
African American	2 (16.7)	0	1.66	.49
Asian American	1 (8.3)	0	0.79	1.00
Socioeconomic status, mean (± SD) ^a	2.9 (1.5)	2.2 (0.8)	1.27	.22
Abuse history related to PTSD, N (%)				
Emotional	8 (66.7)	5 (54.5)	0.27	.67
Verbal	6 (50.0)	7 (77.8)	1.68	.37
Physical	6 (50.0)	4 (44.4)	0.64	1.00
Sexual	10 (83.3)	6 (66.7)	0.79	.61
Rating scale, mean (± SD)				
CAPS-1 total score	65.5 (13.2)	73.9 (10.4)	1.57	.13
CAPS-2 total score	63.5 (17.4)	65.6 (13.8)	0.29	.77
HAM-D	21.5 (7.3)	16.1 (7.5)	-1.66	.11
HAM-A	1.56 (0.48)	1.47 (0.46)	-0.40	.69
Dissociative Experiences Scale	13.1 (9.7)	14.9 (10.3)	0.41	.69

^aDetermined using the Hollingshead Redlich Scale.³²

Abbreviations: CAPS-1 = Clinician-Administered PTSD Scale, 1-month version; CAPS-2 = Clinician-Administered PTSD Scale, 1-week version; HAM-A = Hamilton Rating Scale for Anxiety; HAM-D = Hamilton Rating Scale for Depression; PTSD = posttraumatic stress disorder.

Table 2. Baseline DSM-III-R Psychiatric Comorbidity in Women With PTSD Related to Childhood Abuse

Diagnosis	Risperidone $(N = 12)$	Placebo (N = 9)
Major depression	8	5
Dysthymia	1	0
Panic disorder	3	1
Agoraphobia with panic disorder	2	0
Agoraphobia without panic disorder	1	0
Generalized anxiety disorder	1	2
Simple phobia	3	0
Social phobia	0	1
Eating disorder NOS	1	0
Obsessive-compulsive disorder	0	1
Somatization disorder	1	0
Abbreviation: $NOS = not$ otherwise specification $NOS = not$	fied.	

squares modeling).²⁷ In applying this method, which included time as a covariate, subjects were defined as the random effect and the drug versus placebo contrast as a fixed effect. This method is tolerant of missing data and of heteroscedasticity across subjects. Model fit was checked by examining model residuals graphically. Last-observation-carried-forward (LOCF) methods were used for some contrasts. Statistical significance required p < .017, adjusted using the Boneferroni method to account for multiple comparisons.

RESULTS

Sample Description

Twenty-one subjects enrolled in the study. Twelve subjects were randomly assigned to risperidone; 9 subjects were randomly assigned to placebo. Nine subjects in the risperidone group and 7 subjects in the placebo group

completed 8 weeks of the study. Table 1 shows baseline clinical characteristics of each treatment group. There were no significant differences between the risperidone and placebo groups with respect to any of the baseline measures.

As shown in Table 2, major depression was the most common comorbid psychiatric disorder for both treatment groups. Eight patients in the risperidone group and 5 patients in the placebo group met DSM-III-R criteria for this disorder. There were no statistically significant differences between the 2 groups in psychiatric comorbidity.

Nine subjects, 5 in the risperidone group and 4 in the placebo group, were taking other psychiatric medications during the study. Four subjects in the risperidone group were taking an SSRI, 1 was taking a tricyclic, and 2 were taking benzodiazepines. Two subjects in the placebo group were taking an SSRI, 1 was taking a tricyclic, 1 was taking a benzodiazepine, and 1 was taking trazodone.

The overall mean dosage of risperidone prescribed in the study was 1.41 mg. The weekly mean dosages were 0.77 mg at week 1, 1.47 mg at week 2, 1.83 mg at week 4, and 2.05 mg at week 8. No specific dosage of risperidone correlated significantly with reduction in the total CAPS-2 score. In addition, there was no minimum risperidone dosage identifiable at which mean reductions in the CAPS-2 total score began to differ between risperidone and placebo groups.

Efficacy

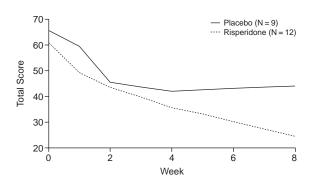
Table 3 shows mean changes from baseline in the CAPS-2 for the risperidone and placebo groups. The mean reduction in the total CAPS-2 scores aggregated over all assessment periods was significantly

Table 3. Changes From Baseline in CAPS-2 Scores of Women With PTSD Related to Childhood Abuse

	Risperidone (N = 12)		Placebo (N = 9)		z Statistic ^b for	p Value ^c for
CAPS-2	Mean Change ^a	SD	Mean Change ^a	SD	Active Drug, Time	Active Drug, Time
Total score	-29.6	31.5	-18.6	12.3	-2.44, -4.32	.015, < .001
Intrusive subscale score	-7.1	9.6	-3.3	4.9	-5.71, -3.76	< .001, < .001
Avoidant subscale score	-10.4	14.9	-8.9	7.4	0.17, -3.08	.866, .002
Hyperarousal subscale score	-12.1	12.1	-6.3	7.5	-2.74, -4.10	.006, < .001

^aLast-observation-carried-forward methods used to estimate mean changes

Figure 1. Mean CAPS-2 Total Score Over Time by Active Drug vs. Placebo in Women With PTSD Related to Childhood Abuse



Abbreviations: CAPS-2 = Clinician-Administered PTSD Scale, 1-week version; PTSD = posttraumatic stress disorder.

greater for subjects receiving risperidone compared with subjects receiving placebo. On the CAPS-2 total score, the risperidone subgroup change at endpoint was 29.6 points (LOCF), while the placebo group change was 18.6 points. The difference of more than 50% in change from baseline was strongly statistically significant (z = -2.44, p = .015). Similarly, subjects randomly assigned to risperidone experienced much larger change in score from baseline on the CAPS-2 intrusive and hyperarousal subscales. For both of these subscales, the risperidone change from baseline was more than twice as large as the comparable change from baseline experienced by placebo subjects. Both of these differences were strongly statistically significant (z = -5.71, p < .001 and z = -2.74, p = .006, respectively). The mean reduction in score on the avoidant subscale of the CAPS-2 did not differ significantly between the risperidone and placebo groups.

Mean changes over time on CAPS-2 total score for the placebo and risperidone subgroups are shown graphically in Figure 1. It is clear that, for the risperidone subgroup, PTSD symptoms severity, as assessed by the CAPS-2 instrument, decreased steadily throughout the duration of the intervention. In contrast, for the placebo subjects there was a decline-in-parallel with the active drug group for the first 2 weeks of the study (placebo effect) and then a leveling-off in weeks 4 through 8. As noted above, the differences reflected in the line graphs in Figure 1 are strongly statistically significant (z = -2.44, p = .015).

Neither the mean change in the CAPS-1 total score nor the mean changes in any of the CAPS-1 subscale scores differed significantly between the risperidone and placebo groups. Response to risperidone did not correlate significantly with type of abuse, age at onset of abuse, or duration of abuse.

Safety

Treatment-emergent adverse events were reported by 4 subjects in the risperidone group and by 1 subject in the placebo group. Adverse events in the risperidone group included sedation, dry mouth, tremor, apathy, and poor concentration. The only adverse event reported in the placebo group was sedation. Only 1 subject in the risperidone group discontinued the study early because of an adverse event—apathy with poor concentration. The mean prolactin level of subjects receiving risperidone increased by 26.2 ng/mL; the mean prolactin level of subjects receiving placebo decreased by 1 ng/mL. This difference was statistically significant (z = 10.8, p < .001). No subjects reported adverse events that appeared related to an increase in prolactin. Subjects receiving risperidone had a mean increase in weight of 2.5 lb (1.1 kg) (SD = 4.1 lb [1.9 kg]); subjects receiving placebo had a mean increase in weight of 3 lb (1.4 kg) (SD = 6.2 lb [2.8 kg]). This difference was not statistically significant.

DISCUSSION

The results of this preliminary study indicate that risperidone is a safe and effective treatment for PTSD related to childhood physical, sexual, emotional, and verbal abuse in women. The results show that risperidone is specifically effective in the alleviating the intrusive and hyperarousal symptoms associated with PTSD in this population.

In our study, the mean changes from baseline in the CAPS-2 total score, as well as in the intrusive and hyperarousal subscale scores of the CAPS-2, differed signifi-

^bz Statistics obtained using random effects regression modeling methods. First z statistic is for drug effects; second is for time. ^cWhen adjusted for multiple comparisons using Bonferroni method (with adjusted p value = .017), changes in CAPS-2 total, CAPS-2 intrusive, and CAPS-2 hyperarousal scores remain statistically significant. First p value is for drug effects; second is for time.

Abbreviations: CAPS-2 = Clinician-Administered PTSD Scale, 1-week version; PTSD = posttraumatic stress disorder

cantly between the risperidone and placebo groups, but mean changes from baseline in the CAPS-1 total score and CAPS-1 subscale scores did not differ significantly between the 2 groups. This may, in part, have been due to the fact that CAPS-1 data were available at only 1 timepoint after baseline, whereas CAPS-2 data were available at 4 timepoints after baseline over the course of the study.

The dosages of risperidone used in this study were approximately half those recommended as the target dosage for schizophrenia.²⁸ The average dosage of risperidone used overall was 1.41 mg; the average dosage used at the end of the study was 2.05 mg. These are similar to dosages previously reported effective in the treatment of PTSD.^{15–17} Although our results suggest that low dosages of risperidone are effective in treating PTSD, they do not provide any evidence that there is a particular threshold dosage at which PTSD symptoms begin to improve significantly.

Our results suggest that risperidone is a safe treatment for PTSD in the population studied. Only 1 subject on risperidone discontinued the study before its endpoint (week 8) because of possible side effects. Although this subject complained of intolerable apathy and poor concentration, it was unclear whether these symptoms were related to risperidone alone, for she was simultaneously experiencing an acute exacerbation of chronic obstructive pulmonary disease, requiring a trial of corticosteroids. Side effects in the other 3 risperidone-treated subjects reporting adverse events resolved quickly, either as the patient adjusted to the medication or as the dosage of risperidone was decreased slightly.

The mechanism by which risperidone reduces both core and associated PTSD symptoms remains unclear. Other investigators have emphasized the effects of atypical antipsychotics on the serotonergic and dopaminergic systems, both of which have been implicated in chronic PTSD through preclinical models of stress responses, ^{12,29} but risperidone also has affinities for α-adrenergic receptors, ³⁰ which have been shown to be dysregulated in PTSD. ³¹ In addition, risperidone may function as a sedative through its antihistaminic properties. ³⁰

Results of the study should be considered preliminary for several reasons. To begin with, the study had a small sample size and was of short duration. Moreover, because almost half the subjects in the study were taking other psychiatric medications, the study must be considered partially one of risperidone as an augmenting agent in the treatment of PTSD. Further studies with a larger sample size and a longer follow-up period are necessary to provide more conclusive evidence of risperidone's effectiveness—either as monotherapy or as an augmenting agent—in the pharmacotherapy of PTSD related to childhood abuse in women.

Because PTSD occurs more commonly in women and our study sample was small, we limited subjects only to women. Further research is needed to determine whether risperidone is effective in men with PTSD related to childhood abuse.

To our knowledge, this study is the first placebocontrolled study of the atypical antipsychotic treatment of PTSD related to childhood abuse in women. For this reason, results of the study are difficult to compare precisely with those of other recent studies. Nevertheless, our findings are consistent with those of previous placebocontrolled studies of risperidone treatment of combatrelated PTSD in showing risperidone to be effective in reducing symptoms of both intrusion and hyperarousal. ^{15–17}

Drug names: benztropine (Cogentin and others), bupropion (Wellbutrin and others), clozapine (Clozaril, Fazaclo, and others), diphenhydramine (Benadryl and others), mirtazapine (Remeron and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trazodone (Desyrel and others), venlafaxine (Effexor), zolpidem (Ambien).

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