Risperidone in Psychotic Combat-Related Posttraumatic Stress Disorder: An Open Trial

Dragica Kozarić-Kovačić, M.D., Ph.D.; Nela Pivac, D.V.M., Ph.D.; Dorotea Mück-Šeler, B.Sc., Ph.D.; and Barbara Olasov Rothbaum, Ph.D.

Rationale: Psychotic symptoms that frequently occur in combat-related posttraumatic stress disorder (PTSD) complicate its pharmacotherapy. We hypothesized that war veterans with psychotic PTSD, resistant to prior antidepressant treatment, would respond well to 6 weeks of treatment with the atypical antipsychotic risperidone, given as a monotherapy.

Method: Twenty-six male war veterans with psychotic PTSD (DSM-IV) completed the 6-week inpatient treatment with risperidone (2–4 mg/day) during the period from November 1999 through December 2002. The primary outcome measure was change from baseline to endpoint (6 weeks) in Positive and Negative Syndrome Scale (PANSS) total and subscale scores. Secondary outcome measures were changes in PTSD Interview (PTSD-I) and Clinical Global Impressions-Severity of Illness scale (CGI-S) total and subscale scores. Clinical improvement was assessed by CGI-S, CGI-Improvement scale, and Patient Global Impression of Improvement scale, while adverse events were recorded by Drug-Induced Extrapyramidal Symptoms Scale.

Results: Treatment with risperidone for either 3 or 6 weeks in an open trial significantly reduced total and subscales scores on the PANSS and on the PTSD-I and CGI-S when compared to baseline scores in patients with psychotic PTSD.

Conclusion: Our preliminary data from the open trial indicate that risperidone decreased most of the psychotic and PTSD symptoms. Psychotic PTSD patients, unresponsive to antidepressant treatment, improved significantly after treatment for either 3 or 6 weeks with risperidone.

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Received July 22, 2004; accepted Jan. 1, 2005. *From the National Centre for Psychotrauma, Department of Psychiatry, Dubrava University Hospital, Zagreb, Croatia (Dr. Kozarić-Kovačić); the Division of Molecular Medicine, Rudjer Bošković Institute, Zagreb, Croatia (Drs. Pivac and Mück-Šeler); and The Emory Clinic, Department of Psychiatry, Atlanta, Ga. (Dr. Rothbaum).*

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Corresponding author and reprints: Nela Pivac, D.V.M., Ph.D., Rudjer Bošković Institute, Division of Molecular Medicine, P.O. Box 180, HR-10002 Zagreb, Croatia (e-mail: npivac@irb.hr).

Risperidone is an atypical antipsychotic that has affinity for 5-HT_{2A}, 5-HT_7, D_2, α_1, and α_2 receptors.[1] Risperidone reduces positive symptoms (delusions, hallucinations, thought disorder, excitement, and hostility), negative symptoms (social and emotional withdrawal, apathy, and difficulty in abstract thinking), aggression, and agitation and improves participation in social activities in psychotic patients.[2]

Psychotic combat-related posttraumatic stress disorder (PTSD) is a severe form of PTSD.[3–6] PTSD is usually treated pharmacologically with antidepressants, adrenergic and antianxiety agents, and mood stabilizers.[7–11] The presence of psychotic symptoms in PTSD[3,4,12–17] is often associated with treatment resistance and requires additional pharmacologic strategies, such as the use of neuroleptics or atypical antipsychotics.[7,11] There are only a few studies reporting the use of different neuroleptics[13,17,18] or antipsychotics like risperidone,[19–22] olanzapine,[17,23–27] or quetiapine[28,29] in the treatment of PTSD. Among them, some reports describe the effects of antipsychotics on civilian PTSD subjects.[13,21,24,25] The effects of risperidone in PTSD were described in a series of case reports.[19,21,30,31] Since the studies evaluating the effects of the atypical antipsychotic risperidone in psychotic PTSD are still extremely scarce, or participants in these studies also received additional medication,[20,22] the aim of the present open clinical trial was to evaluate, in a naturalistic setting, the effects of 3 and 6 weeks of treatment with the atypical antipsychotic risperidone (2–4 mg/day), given as a monotherapy, in a large group of well-characterized male war veterans with psychotic PTSD.

METHOD

Participants

Twenty-seven subjects were entered into and 26 completed the 6-week study. All participants were white Croatian male war veterans, aged 28 to 48 years, who were hospitalized at the National Center for Psychotrauma of the University Hospital Dubrava, Zagreb, Croatia, during the period from November 1999 through December 2002. The diagnosis of current and chronic psychotic PTSD was made according to the Structured Clinical Interview for DSM-IV (SCID),[32] the Clinician-Administered PTSD Scale (CAPS),[33] the PTSD Interview (PTSD-I),[34] and

the Hamilton Rating Scale for Depression (HAM-D).[35] The evaluations and ratings were performed by psychiatrists (one of them is the author D.K.K.) who are very clinically experienced in the field of psychotrauma. The interrater reliability was 0.92%. Psychotic symptoms were defined as evidence for hallucinations or delusions on the psychotic module of the SCID or specific disturbance in form of thoughts by mental status examination.

Patients were war veterans who spent their active duty in the Croatian armed forces (1–4 years; most had 3 years of continuous combat experience), had similar social and cultural backgrounds, and were mostly married. The inclusion criteria were current and chronic psychotic PTSD and refractoriness to antidepressant therapy in the previous 12 months.

During a 12-month period, 22 patients were treated with selective serotonin reuptake inhibitors (but not with fluoxetine), 15 with tricyclic antidepressants, 7 with other antidepressants, 15 with sedative hypnotics, and 8 with anticonvulsants. Since there was no improvement in the symptoms, and in 8 patients the clinical symptoms worsened, they were offered participation in the current study. Washout was 2 weeks. During this period patients used 10 mg of diazepam. All patients were screened in a comprehensive multidisciplinary evaluation (conducted by 2 psychiatrists and a psychologist) prior to entry into inpatient treatment. Subjects were excluded if they had a positive family history of psychosis; a history of schizophrenia, schizoaffective disorder, or bipolar disorder; a serious concomitant medical condition; a history of seizures or misuse of alcohol or drugs (recent use of any psychotropic drugs within 1 month of baseline); clinically significant abnormalities in electrocardiogram or laboratory findings; or a serious risk of suicide. To exclude comorbidity with major depressive disorder, which can be comorbid with nonpsychotic or psychotic PTSD, only patients with total scores of 18 or lower on the HAM-D were included in the study.

Psychotic symptoms were defined as evidence of hallucinations or delusions during the mental status examination and were scored as at least 4 (moderate severity) on the 4 critical positive items on the Positive and Negative Syndrome Scale (PANSS)[36] (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution), 2 negative items (emotional withdrawal and passive/apathetic social withdrawal), 8 items of the general psychopathology subscale (guilt feelings, depression, motor retardation, unusual thought content, disorientation, disturbance of volition, poor impulse control, and active social avoidance), and 2 items on the supplementary subscale (anger and affective lability). Psychotic symptoms were more strongly associated with characteristics of combat-related PTSD than with characteristics of psychosis or major depressive disorder with psychotic features.

Combat-related symptoms included images of screaming soldiers, fire, bombing, and rocketing. A psychotic PTSD subtype consisted of cases with primary PTSD and secondary psychotic symptoms in which the onset of PTSD preceded the onset of psychosis and patients did not have earlier thought disorder or bizarre behavior. Patients were excluded if psychotic symptoms occurred only during a flashback or dissociative episode.

Psychotic symptoms presented as 3 clinical pictures. (1) Symptoms were schizophrenia-like in 7 patients (27%), characterized mostly by conceptual disorganization, delusions, and suspiciousness/persecution. The content of delusions and suspiciousness/persecution was connected with the paranoid fear that enemies were trying to kill them, so very often they woke up during the night and stayed on a watch. Visual hallucinations were mostly connected with the scenes of war, ugly faces of dead people and slaughtered bodies, olfactory hallucinations with smell of massacred and disintegrated bodies, and auditory hallucinations with screaming soldiers and sounds of shell and rocket fire. (2) Symptoms were psychotic depression–like in 10 patients (38%), characterized mostly by hallucinatory behavior, depressive psychotic accusations, depressive delusions of guilty feelings related to feelings of guilt because their comrades were killed in battle, and imaginary accusations by the family members of their slain comrades. (3) Symptoms were of a mixed clinical picture in 9 patients (35%), characterized by conceptual disturbances and disorganization, persecutive and depressive delusions, and visual, auditory, and olfactory hallucinations.

The procedure was fully explained, and written informed consent was obtained from all patients. The study was approved by the ethics committee of the Dubrava University Hospital, Zagreb, Croatia.

Study Design

The study design was open: 27 veterans received 2 to 4 mg/day of risperidone monotherapy (mean dose = 3.46 mg, SD = 0.90 mg), and 26 patients (96%) finished the 6-week treatment. Seven patients (27%) received 2 mg of risperidone for 6 weeks, and 19 patients (73%) received 4 mg, with a starting dose of 2 mg of risperidone once daily, increased during the first week up to 4 mg every 2 days. Later, the dose of 4 mg of risperidone was given as 2 mg twice a day. The only concomitant psychotropic medication allowed during the study was zolpidem, and biperiden was allowed for side effects. All patients received zolpidem as needed during the 6-week study. Only 1 patient dropped out of the study at the beginning, due to personal reasons unrelated to the study medication, and therefore, his data were excluded.

Measures

Psychotic PTSD diagnoses were made independently by 2 psychiatrists on the basis of the SCID. The subjects were asked to describe their traumatic experiences and

Table 1. Clinical Rating Scale Responses at Baseline and After 3 and 6 Weeks of Treatment With Risperidone in 26 War Veterans With Psychotic Combat-Related Posttraumatic Stress Disorder (PTSD)

Scale	Before Treatment, Mean (SD)	After 3 Weeks, Mean (SD)	After 6 Weeks, Mean (SD)	F (df = 2,25; p < .001)	Decline From Baseline, %
PANSS					
Total	135.5 (9.1)*	53.9 (4.5)	51.9 (3.8)	2145.0	62
Positive	31.9 (4.7)*	11.2 (1.7)	10.8 (1.5)	511.4	66
Negative	30.6 (5.6)*	10.0 (1.7)	9.9 (1.5)	399.0	68
General psychopathology	58.6 (8.4)*	27.2 (3.4)	26.0 (3.4)	1458.4	56
Supplementary items	13.1 (2.1)*	5.5 (1.2)	5.2 (1.1)	419.4	60
PTSD-I					
Total	101.6 (6.5)*	40.1 (4.0)	38.2 (3.6)	1598.4	62
Reexperiencing	22.9 (1.8)*	10.6 (1.7)	10.2 (1.4)	724.4	44
Avoidance	38.0 (3.6)*	16.5 (2.1)	15.6 (2.2)	541.1	59
Hyperarousal	41.1 (3.3)*	13.1 (2.6)	12.4 (2.4)	1108.3	70
CGI-S	5.8 (0.4)*	2.4 (0.6)	2.2 (0.4)	809.0	62

*p < .05 vs. scores after 3 and after 6 weeks (repeated-measures analysis of variance followed by Tukey test).
Abbreviations: CGI-S = Clinical Global Impressions-Severity of Illness scale, PANSS = Positive and Negative Syndrome Scale, PTSD-I = PTSD Interview.

were given enough time to talk about these and other psychiatric disturbances. Current PTSD was assessed with the CAPS[33] and also with the PTSD-I[34] based on DSM-III-R, translated into Croatian, and standardized on the Croatian population[37,38] (psychometric characteristics of the PTSD-I: internal consistency, alpha = 0.92; test-retest reliability, r = 0.95). The results are shown only for the PTSD-I, because this scale was standardized on the Croatian population.[37,38] The total scores on the CAPS (mean = 103.9, SD = 7.8) were not significantly (t = 1.155, df = 50, p > .05, Student t test) different from the total scores on the PTSD-I at screening.

The primary measure of efficacy was the change from baseline to endpoint (6 weeks) in PANSS[36] total and subscales scores. At baseline and after 3 and 6 weeks of treatment, secondary outcome measures, i.e., PTSD-I and Clinical Global Impressions-Severity of Illness scale (CGI-S),[39] were administered by the same psychiatrists, assessing PTSD symptoms and clinical improvement. After 3 and 6 weeks, symptoms were evaluated by the Clinical Global Impressions-Improvement scale (CGI-I),[39] Patient Global Impression of Improvement scale (PGI-I),[39] and Drug-Induced Extrapyramidal Symptoms Scale (DIEPSS).[40] Adverse events were recorded after 3 and 6 weeks of treatment using the DIEPSS, and spontaneously reported adverse effects were recorded during the trial.

Statistical Analysis

The statistical analysis of the data was conducted with SigmaStat 2.0 (Jandel Scientific Corp., San Rafael, Calif.). The results were evaluated using repeated-measures 1-way analysis of variance (ANOVA) followed by Tukey multiple comparison test. Pearson coefficient of correlation was used to test the correlation between 2 variables. Paired Student t test was used to compare 2 variables only. The alpha level was set at p < .05.

RESULTS

Twenty-six psychotic PTSD subjects were treated with risperidone for 6 weeks. The mean age was 36.9 years (SD = 4.0), and the mean duration of combat experience was 3.0 years (SD = 0.94).

Three or 6 weeks of treatment with risperidone was associated with significant reductions (a decline in baseline scores of 44%–70%) in total and subscales scores on the PANSS, PTSD-I, and CGI-S in psychotic PTSD subjects (Table 1). ANOVAs revealed that total and subscales scores on positive, negative, general psychopathology, and supplementary items of the PANSS; total and subscale scores on trauma reexperiencing, avoidance, and hyperarousal on the PTSD-I; and total scores on the CGI-S were all significantly (p < .05, Tukey test) lower after 3 and 6 weeks of risperidone treatment than at baseline. The scores on all measurement instruments were similarly reduced (p > .05, Tukey test) after 3 as well as after 6 weeks of treatment. There was no significant difference (p > .05, paired t test) between the scores on the CGI-I, PGI-I, or DIEPSS after 3 and after 6 weeks of treatment with risperidone (Table 2). No significant correlation was found between PANSS positive and PTSD-I trauma reexperiencing symptoms (r = 0.172; p = .401), between PANSS positive and PTSD-I hyperarousal symptoms (r = –0.170; p = .408), or between PANSS negative and PTSD-I avoidance symptoms (r = –0.073; p = .723).

Extrapyramidal side effects, mostly akathisia (8 patients), psychomotor agitation (7 patients), and rigor (11 patients), appeared in 11 (42%) of the patients who were prescribed biperiden in the 2- to 4-mg/day dose range. One patient received 4 mg of biperiden, and the rest (10 patients) were given 2 mg of biperiden. Other side effects were sedation in 9 patients (35%) and anxiety in 12 patients (46%). Five patients (19%) had slightly in-

creased appetite, and weight gain up to 4 kg was observed in 3 patients (12%) during 6 weeks of treatment.

DISCUSSION

The data from our open clinical trial have shown that treatment with risperidone, given as a monotherapy, was associated with substantial improvement in 26 war veterans with psychotic PTSD. The clinical response of our psychotic PTSD patients to 6-week monotherapy with risperidone was significant, as seen in greatly reduced total (62%) and subscales scores (56%–68%) of the PANSS and total (62%) and subscales scores (44%–70%) of the PTSD-I scale. Our data also showed no significant differences between response at 3 and 6 weeks of risperidone treatment. The psychotic symptoms, including conceptual disorganization, delusions and suspiciousness/persecution, hallucinatory behavior, depressive psychotic accusations, depressive delusions, conceptual disturbances and disorganization, persecutive and depressive delusions, visual and auditory hallucinations, and core PTSD symptoms, were all affected similarly at other time points.

Although there have been a few positive studies describing the effect of risperidone in the treatment of PTSD, our study is the first one that evaluates the effects of a monotherapy with risperidone in a well-characterized ethnically and racially uniform group of war veterans with psychotic PTSD, who did not have any other comorbidities and/or any other additional medication. The only additional psychotropic medication was zolpidem, but since all patients sporadically received zolpidem during the 6 weeks of treatment, the possible effect of zolpidem on the clinical response might be negligible.

Our results are consistent with the data from the previous studies.[20,22] However, in contrast to the patients included in our study, the patients in the study of Hamner et al.[22] comprised PTSD subjects with other comorbid Axis I diagnoses, mostly major depression, but also other anxiety disorders and history of substance abuse in remission,[22] and most of the patients in both studies were taking antidepressants.[20,22] In our study, risperidone monotherapy was associated with significant decreases in the positive, negative, general psychopathology, and supplementary items of the PANSS subscales and PTSD-I trauma reexperiencing, avoidance, and hyperarousal subscales.

In agreement with our finding that risperidone monotherapy reduced most of the PTSD and psychotic symptoms when compared to scores and/or symptoms before treatment, low doses of risperidone given as adjunctive therapy have been reported to reduce irritability and intrusive thoughts in 7 combat veterans with PTSD.[41] In case reports, risperidone has been reported to have a possible beneficial effect, given alone[21] or with additional antidepressants: in 4 cases of physical trauma patients,[21] in 2 PTSD patients,[19] in 4 cases of PTSD associated with major depression,[31] and in a case report of combat trauma.[30] Hence the data from the present study, obtained from a fairly large group (N = 26) of drug-free ethnically and racially uniform male war veterans with psychotic PTSD, support risperidone's role as a monotherapy in the management of severe psychotic PTSD that is resistant to prior antidepressant treatment.[11]

Table 2. Rating Scale Scores After 3 and 6 Weeks of Treatment With Risperidone in 26 War Veterans With Psychotic Combat-Related Posttraumatic Stress Disorder

Scale	After 3 Weeks, Mean (SD)	After 6 Weeks, Mean (SD)	Paired t test t	p
CGI-I	1.8 (0.7)	1.6 (0.6)	1.55	.134
PGI-I	1.7 (0.6)	1.7 (0.5)	0.44	.664
DIEPSS	0.9 (0.9)	1.0 (1.0)	–1.16	.256

Abbreviations: CGI-I = Clinical Global Impressions-Improvement scale, DIEPSS = Drug-Induced Extrapyramidal Symptoms Scale, PGI-I = Patient Global Impression of Improvement scale.

Patients' impression of their improvement was similar to that observed by clinicians, as shown in similarly decreased scores on CGI-I and PGI-I scales. Reported side effects consisted of akathisia, psychomotor agitation, and rigor (42%); sedation (35%); and anxiety (46%). These patients were treated with biperidone. A slight increase in appetite was observed in 19% of patients, and weight gain up to 4 kg was observed in 11% of patients (during 6 weeks of treatment). However, these mild side effects did not lead to any dropouts. The only dropout was unrelated to study medication.

Our results are supported also by the data showing a great improvement in psychotic PTSD symptoms obtained after treatment with other atypical antipsychotic drugs, olanzapine[17,24–27] and quetiapine,[28,29] in war veterans with psychotic PTSD,[17] in combat-related PTSD,[26,27] and in civilian PTSD.[24,25]

Inconsistent with our data, traditional antipsychotics[13,18,42] and olanzapine[23] failed to significantly affect PTSD symptoms. It is difficult to compare the results of the previous studies with our study, since there are differences in the drugs used, design, duration, diagnoses, and inclusion criteria (civilian trauma victims vs. war veterans) between the studies. However, our results have shown that risperidone (present study), olanzapine,[17] or fluphenazine,[17] given as monotherapy, alleviated most of the PTSD and psychotic symptoms in war veterans with psychotic PTSD who were resistant to antidepressant treatment. The findings from the present and previous[17] studies have shown that prolongation of the treatment for an additional 3 weeks did not affect the improvement seen after 3 weeks. Similar to the results of our previous study,[17] we failed to detect significant correlations between the PANSS positive and PTSD-I trauma reexperiencing symptoms and between the PANSS negative and PTSD-I avoid-

ance symptoms. These data suggest that psychotic PTSD occurring in our war veterans might represent a distinct, i.e., psychotic, subtype of PTSD.[4] Hallucinations were not limited only to reexperiencing the traumatic event, since PANSS positive and trauma reexperiencing scores were not correlated, and patients included in our study did not have psychosis, schizophrenia, schizoaffective disorder, or bipolar disorder prior to PTSD. In addition, negative symptoms, which can share similarities with depressive symptoms, were not related to avoidance symptoms, indicating that psychotic symptoms in our PTSD subjects could not be attributed only to comorbid depression. The lack of association between hyperarousal symptoms and PANSS positive symptoms in the present study also supports the hypothesis that psychotic PTSD is a separate subtype, because hyperarousal symptoms can also be related to paranoia and other psychotic symptoms. Although the presence of psychotic features in PTSD might indicate previous comorbidity,[4,22,29] our inclusion/exclusion criteria excluded patients with previous Axis I disorders. The data from our previous[16,17,43] and present studies indicate that a large percentage of Croatian war veterans have psychotic PTSD. Our data support the hypothesis that psychotic PTSD is a PTSD subtype.[4,6]

The exact mechanism by which risperidone affects the psychotic symptoms in PTSD is still uncertain. It has high antiserotonergic activity, achieved via 5-HT_{2A} and 5-HT_7 receptors, and antidopaminergic D_2 activity, but it also binds to α_1 and α_2 adrenoceptors[1] and has virtually no relevant affinity for histamine H_1 and muscarinic receptors. This pharmacologic profile enables risperidone to modulate not only serotonergic and dopaminergic but also noradrenergic neurotransmission, thought to be dysregulated in PTSD. Therefore, risperidone reduces positive and negative symptoms and cognitive and depressive symptoms[2]; alleviates aggression,[41] suicidality, and impulsivity; and has beneficial effects on nightmares and flashbacks. Its antidepressant and antianxiety effects add to its efficacy in psychotic PTSD.

The limitations of the present study were its open design and lack of a comparison drug or a placebo, but the advantages were a naturalistic setting, a prolonged treatment period, monotherapy with risperidone, and the inclusion of a large group of well-characterized male war veterans with combat-related psychotic PTSD, resistant to prior antidepressant treatment. In agreement with the recently proposed pharmacologic strategies,[10,11,44] our data support the use of the atypical antipsychotics as effective monotherapies in the treatment of antidepressant treatment–resistant war veterans with psychotic PTSD.

CONCLUSION

In summary, psychotic PTSD patients receiving risperidone for 3 or 6 weeks in an open study improved significantly. Risperidone significantly reduced most of the PTSD and psychotic symptoms. The occurrence of mild side effects did not lead to dropouts in our psychotic PTSD patients. Our results, obtained from a large group of treatment-resistant war veterans with psychotic PTSD, indicate that risperidone is effective in the treatment of psychotic PTSD symptoms.

Drug names: biperiden (Akineton), diazepam (Valium and others), fluoxetine (Prozac and others), fluphenazine (Prolixin and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), zolpidem (Ambien).

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