Pharmacotherapy of Treatment-resistant Combat-related Posttraumatic Stress Disorder with Psychotic Features

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Aim To assess retrospectively the clinical effects of typical (fluphenazine) or atypical (olanzapine, risperidone, quetiapine) antipsychotics in three open clinical trials in male Croatian war veterans with chronic combat-related posttraumatic stress disorder (PTSD) with psychotic features, resistant to previous antidepressant treatment.

Methods Inpatients with combat-related PTSD were treated for 6 weeks with fluphenazine (n = 27), olanzapine (n = 28), risperidone (n = 26), or quetiapine (n = 53) as a monotherapy. Treatment response was assessed by the reduction in total and subscales scores in the clinical scales measuring PTSD (PTSD interview and Clinician-administered PTSD Scale) and psychotic symptoms (Positive and Negative Syndrome Scale).

Results After 6 weeks of treatment, monotherapy with fluphenazine, olanzapine, risperidone, or quetiapine in patients with PTSD significantly decreased the scores listed in trauma reexperiencing, avoidance, and hyperarousal subscales in the clinical scales measuring PTSD, and total and subscales scores listed in positive, negative, general psychopathology, and supplementary items of the Positive and Negative Syndrome Scale subscales, respectively ($P<0.001$).

Conclusion PTSD and psychotic symptoms were significantly reduced after monotherapy with typical or atypical antipsychotics. As psychotic symptoms commonly occur in combat-related PTSD, the use of antipsychotic medication seems to offer another approach to treat a psychotic subtype of combat-related PTSD resistant to previous antidepressant treatment.

In a world in which terrorism and conflicts are constant threats, and these threats are becoming global, posttraumatic stress disorder (PTSD) is a serious and global illness. According to the criteria from the 4th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) (1), exposure to a life-threatening or horrifying event, such as combat trauma, rape, sexual molestation, abuse, child maltreatment, natural disasters, motor vehicle accidents, violent crimes, hostage situations, or terrorism, can lead to the development of PTSD (1,2). The disorder may also be precipitated if a person experienced, saw, or learned of an event or events that involved actual or threatened death, serious injury, or violation of the body of self or others (3,4). In such an event a person's response can involve intense fear, helplessness, or horror (3,4). However, not all persons who are exposed to a traumatic event will develop PTSD. Although the stress reaction is a normal response to an abnormal situation, some extremely stressful situations will in some individuals overwhelm their ability to cope with stress (5).

PTSD is a chronic psychiatric illness. The essential features of PTSD are the development of three characteristic symptom clusters in the aftermath of a traumatic event: re-experiencing the trauma, avoidance and numbing, and hyperarousal (1,6). The core PTSD symptoms in the re-experiencing cluster are intrusive memories, images, or perceptions; recurring nightmares; intrusive daydreams or flashbacks; exaggerated emotional and physical reactions; and dissociative experiences (1,6,7). These symptoms intensify or re-occur upon exposure to reminders of the trauma, and various visual, auditory, or olfactory cues might trigger traumatic memories (3,4). The avoidance and numbing cluster of symptoms includes efforts to avoid thoughts, feelings, activities, or situations associated with the trauma; feelings of detachment or alienation; inability to have loving feelings; restricted range of affect; loss of interest; and avoidance of activity. The hyperarousal cluster includes exaggerated startle response, hyper-vigilance, insomnia and other sleep disturbances, difficulties in concentrating, and irritability or outbursts of anger. PTSD criteria include functional impairment, which can be seen in occupational instability, marital problems, discord with family and friends, and difficulties in parenting (3,4,8). In addition to this social and occupational dysfunction, PTSD is often accompanied by substance abuse (9) and by various comorbid diagnoses, such as major depression (10), other anxiety disorders, somatization, personality disorders, dissociative disorders (7,11), and frequently with suicidal behavior (12). Combat exposure can precipitate a more severe clinical picture of PTSD, which may be complicated with psychotic features and resistance to treatment. War veterans with PTSD have a high risk of suicide, and military experience, guilt about combat actions, survivor guilt, depression, anxiety, and severe PTSD are significantly associated with suicide attempts (12).

The pharmacotherapy treatment of PTSD includes the use of antidepressants, such as selective serotonin reuptake inhibitors (fluvoxamine, fluoxetine, sertraline, or paroxetine) as the first choice of treatment, tricyclic antidepressants (desipramine, amitriptyline, imipramine), monoamine oxidase inhibitors (phenelzine, brofaromine), buspirone and other antianxiety agents; benzodiazepines (alprazolam), and mood stabilizers (lithium) (13-16). Although the pharmacotherapy of PTSD starts with antidepressants, in treatment-refractory patients a new pharmacological approach is required to obtain a response. In treatment-resistant patients, pharmacotherapy strategies reported to be effective include anticonvulsants, such as carbamazepine, gabapentine, topiramate, tiagabine, divalproex, lamotrigine (14,17); anti-adrenergic agents, such as clonidine (although presynaptic α2-adrenoceptor agonist, clonidine blocks central noradrenergic outflow from the locus ceruleus), propranolol, and prazo-

sin (13,14), opiate antagonists (13), and neuroleptics and antipsychotics (14,17,18).

Combat exposure frequently induces PTSD, and combat-related PTSD might progress to a severe form of PTSD, which is often refractory to treatment (19-21). Combat-related PTSD is frequently associated with comorbid psychotic features (11,14,17,19-21), while psychotic features add to the severity of symptoms in combat-related PTSD patients (19,22-24). These cases of a more severe subtype of PTSD, complicated with psychotic symptoms, require the use of neuroleptics or atypical antipsychotic drugs (14,17,25-27).

After the war in Croatia (1991-1995), an estimated million people were exposed to war trauma and about 10 000 of the Homeland War veterans (15% prevalence) have developed PTSD, with an alarmingly high suicide rate (28). The war in Croatia brought tremendous suffering, not only to combat-exposed veterans and prisoners of war (29), but also to different groups of traumatized civilians in the combat zones, displaced persons and refugees, victims of terrorist attacks, civilian relatives of traumatized war veterans and terrorist attacks victims, and traumatized children and adolescents (30). Among Croatian war veterans with combat-related PTSD, 57-62% of combat soldiers with PTSD met criteria for comorbid diagnoses (8-11), such as alcohol abuse, major depressive disorder, anxiety disorders, panic disorder and phobia, psychosomatic disorder, psychotic disorders, drug abuse, and dementia. In addition to different comorbid psychiatric disorders, a great proportion of war veterans with combat-related PTSD developed psychotic features (8,11,25,26), which consisted of psychotic depressive and schizophrenia-like symptoms (suggesting prominent symptoms of thought disturbances and psychosis). Psychotic symptoms were accompanied by auditory or visual hallucinations and delusional thinking in over two-thirds of patients (25,26). Delusional paranoid symptoms occurred in 32% of patients (25,26). The hallucinations were not associated exclusively with the traumatic experience, while the delusions were generally paranoid or persecutory in nature (25,26). Although psychotic PTSD and schizophrenia share some similar symptoms, there are clear differences between these two entities, since PTSD patients still retain some insight into reality and usually do not have complete disturbances of affect (eg, constricted or inappropriate) or thought disorder (eg, loose associations or disorganized responses).

This proportion of veterans with combat-related PTSD refractory to treatment (18-20) and with co-occurring psychotic symptoms requires additional pharmacological strategies, such as the use of neuroleptics (25) or atypical antipsychotics (14,17,26). Studies evaluating the use of antipsychotics in combat-related PTSD with psychotic features are scarce, and antipsychotics were frequently added to existing medication in the treatment of PTSD.

In this study, we compared retrospectively the clinical effects of four antipsychotic drugs – a neuroleptic drug (fluphenazine) and three atypical antipsychotics (olanzapine, risperidone and quetiapine) – in treatment-resistant male war veterans with combat-related PTSD with psychotic features.

Patients and methods

Patients

The study included Caucasian male war veterans from Croatia, aged between 33 and 51 years (mean±SD age, 38.0 ± 4.7), who were active soldiers in the Croatian armed forces and had on average 3.0 ± 1.0 years of continuous combat experience. The veterans were recruited from the Referral Center of the Ministry of Health and Social Welfare for the Stress-related Disorders, Regional Center for Psychotrauma, Department of Psychiatry, Dubrava University Hospital, from 1998 to 2005. The diagnosis of PTSD was made according to the DSM-IV criteria (1) by use of a structured clinical interview (31).

The screening of the patients included psychiatric, physical, and neurological examinations. The study was approved by the Ethics Committee of the University Hospital Dubrava. The procedure was fully explained and all patients provided written informed consent to the treating psychiatrists. Wash-out was 2-4 weeks. During this period, patients sporadically used up to 10 mg of diazepam.

Inclusion and exclusion criteria

Inclusion criteria. Patients had to be older than 18 years, meet DSM-IV criteria for chronic PTSD, and be able to provide written informed consent. Patients had to present a psychotic PTSD subtype, with psychotic combat-related symptoms, which were secondary to the primary PTSD, and be refractory to antidepressant therapy in the previous 12 months. Refractoriness to treatment was observed in patients who did not respond well in the previous 12 months to treatment with selective serotonin reuptake inhibitors, tricyclic antidepressants, other antidepressants, sedative hypnotics, or anticonvulsants. Patients were considered to be refractory to treatment if they were treated sequentially in two 8-week treatments with different classes of antidepressants without a positive clinical response (worsening of symptoms, no change, or slight improvement). These patients were referred by their local psychiatrist(s) to the Referral Center for the Stress Related Disorders. During these 12 months, patients were treated sporadically or continuously with sedative hypnotics because of the sleep disturbances and nightmares and anticonvulsants in combination with tricyclic antidepressants or selective serotonin reuptake inhibitors or other antidepressants to reduce aggressive behavior. The strategy is that if patients are non-responsive to medication, they are referred from different centers and parts of Croatia to the Referral Center for the Stress Related Disorders. Before enrollment, the patients had been washed out from medication for 4 weeks if they had received fluoxetine, and 2 weeks if they had received other selective serotonin reuptake inhibitors or tricyclic antidepressants or anticonvulsants. Therefore, refractoriness to treatment was not a single failed trial, and most patients had been treated unsuccessfully for a longer period of time before they were referred to the Referral Center for the Stress Related Disorders. In addition, patients had to be free of antipsychotic drugs for at least one month prior to the entry in the study.

Exclusion criteria. Patients were excluded from the study if they had positive family history of psychosis, history of schizophrenia, schizoaffective or bipolar disorder, lifetime schizophrenia, bipolar disorder, or cognitive dysfunction due to a medical condition; past thought disorder or bizarre behavior; history of alcohol or other substance use disorder within 3 months; mental retardation; significant risk of violence or suicide; serious concomitant medical condition; clinically significant abnormalities in electrocardiogram or laboratory findings; including positive urine screen for illicit drugs; history of prior treatment with fluphenazine, olanzapine, risperidone or quetiapine; concomitant therapy with psychotropic medications; need for concurrent psychotherapy; and if the psychotic symptoms occurred only during a flashback or dissociative episode. Psychiatric comorbidity was assessed by means of the Mini-International Neuropsychiatric Interview (MINI) (32). In addition, patients were excluded if they scored 19 or higher on the Hamilton Rating Scale for Depression (33) to exclude the comorbidity with major depression and to ensure that only patients with PTSD with psychotic features were included. However, this criterion may bias the sample as so many patients with PTSD do have comorbid major depression.

Psychotic symptoms

Psychotic symptoms were associated with the traumatic event, ie, they were combat-related: scenes of war; faces of dead people; slaugh-

tered, massacred, and disintegrated bodies; images of screaming soldiers or enemies trying to kill them; sounds of fire, bombing, shell and rocket fire; and so on. Psychotic symptoms were defined as evidence of hallucinations or delusions during the mental status examination, with a score of at least 4 (moderate severity) on the 4 critical positive items on the Positive and Negative Syndrome scale (34) (delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution), 2 negative items (emotional withdrawal, and passive/apathetic social withdrawal), 8 items out 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).

Method

We retrospectively analyzed 3 open-labeled 6-week studies, during which the patients received either fluphenazine (27 patients) or olanzapine (28 patients) 5-10 mg/d, or risperidone (26 patients) 2-4 mg/d, or quetiapine (53 patients) 25-400 mg/d, as a monotherapy. The necessary adjustments of the doses were made, as appropriate, after weekly visits, and clinical response, efficacy, and tolerability of treatment were evaluated weekly. The only concomitant psychotropic medications allowed during the study were zolpidem and biperidone for the side effects.

Outcome measures

The outcome measures used were total and subscale (re-experiencing, avoidance, and hyperarousal) scores on the PTSD interview (35) and the Clinician-administered PTSD scale (36), and total and subscale (positive psychotic symptoms, negative symptoms, global psychopathology, and supplementary items) scores on the Positive and Negative Syndrome scale. The scores were compared to assess the efficacy of different antipsychotic drugs. Since the Clinician-administered PTSD scale and the PTSD interview are both clinical scales measuring PTSD symptoms, with similar questions and scores, the data measuring PTSD symptoms were combined. The PTSD interview was standardized for the Croatian population (37,38) (psychometric characteristics of the Watson's PTSD questionnaire included internal consistency with $\alpha = 0.92$ and test = retest reliability with $r = 0.95$). Clinical improvement was assessed with the Clinical Global Impressions - Severity of Illness scale (39). Safety and tolerability assessments were recorded during weekly visits by the Patient Global Impression Improvement scale and the Drug Induced Extra-pyramidal Symptoms scale (40).

Statistical analysis

Analyzed data were presented as means with standard deviations (mean±SD) and evaluated with one-way analysis of variance (ANOVA), followed by Tukey's multiple comparison tests. $P<0.05$ was considered statistically significant. Statistical analysis was conducted with SigmaStat 2.0 and SigmaStat 3.1 (Jandell Scientific Corp., San Raphael, CA, USA).

Results

Although analysis of variance showed an overall significant effect of age ($P = 0.030$, ANOVA), post-hoc comparison revealed that the age of patients did not significantly differ between groups treated with fluphenazine (38.1 ± 4.8 years), olanzapine (37.2 ± 4.5 years), risperidone (36.9 ± 4.0 years), or quetiapine (39.9 ± 5.5 years) ($P = 0.051$-0.996, Tukey's test). There was no significant difference in duration of combat exposure between PTSD patients treated with fluphenazine (2.9 ± 0.9 years), olanzapine (3.1 ± 0.9 years), risperidone (3.0 ± 1.0 years) or quetiapine (2.9 ± 1.0 years) ($P = 0.841$, ANOVA).

Before treatment with fluphenazine, olanzapine or risperidone, the patient groups did not differ in total PTSD symptom scores ($P = 0.859$-

1.000, Tukey's test; Figure 1). The pretreatment scores in war veterans who received quetiapine therapy for 6 weeks were significantly lower than scores in all other groups of patients (P<0.001, Tukey's test; Figure 1). Six weeks of treatment with fluphenazine, olanzapine, risperidone or quetiapine significantly reduced total (Figure 1) and subscale PTSD symptom scores in trauma reexperiencing (Figure 2), avoidance (Figure 3), and hyperarousal (Figure 4) subscales (P<0.001 for all, Tukey's test). The treatment with fluphenazine or quetiapine equally lowered total PTSD symptom scores by 46% and 41% in comparison with the baseline scores, respectively, while the treatment with olanzapine or risperidone elicited greater reductions of PTSD symptoms by 63% and 62% in comparison with the baseline scores, respectively (Figure 1). The effects of all antipsychotics were comparable on trauma re-experiencing scores (Figure 2). Avoidance scores were equivalently reduced after treatment with fluphenazine and quetiapine (35% and 37% of the baseline scores, respectively), while treatment with olanzapine or risperidone decreased the avoidance scores even more, ie, by 58% and 59% in comparison with the baseline scores, respectively (Figure 3). A significant reduction by 70% from the baseline hyperarousal scores was achieved after olanzapine or risperidone (Figure 4). Treatment with fluphenazine induced a significant (52%) reduction of the baseline scores, while quetiapine treatment decreased the hyperarousal scores by 35% (Figure 4).

Treatment with fluphenazine, olanzapine, risperidone, or quetiapine for 6 weeks significantly decreased total (Figure 5) and subscales scores in positive (Figure 6), negative (Figure 7), general psychopathology (Figure 8), and supplementary items (Figure 9) of Positive and Negative Syndrome scale (P<0.001 for all, Tukey's test). This reduction of the baseline scores was of the similar magnitude after treatment with olanzapine (63%), risperidone (62%), or quetiapine (62%). Fluphenazine treatment induced a slight-

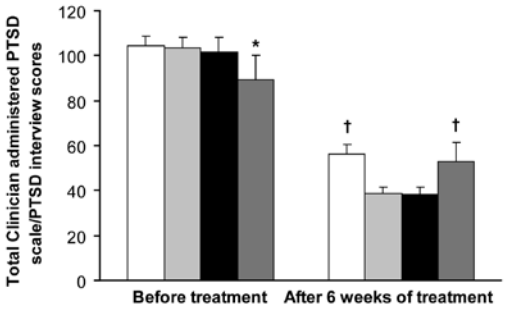

Figure 1. Total posttraumatic stress disorder (PTSD) scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in 134 war veterans with PTSD; P<0.001 for each treatment group before vs after treatment. *P<0.001 vs the scores before treatment with fluphenazine, risperidone, olanzapine (Tukey's test). †P<0.001 vs the scores after 6 weeks of treatment with olanzapine or risperidone.

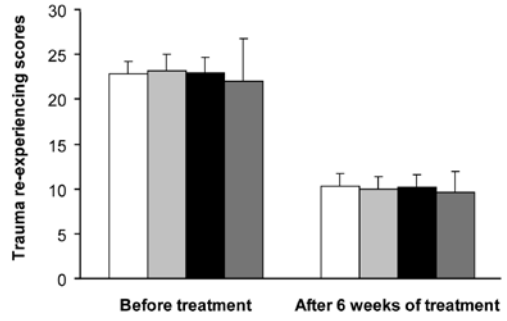

Figure 2. Trauma re-experiencing scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with posttraumatic stress disorder. P<0.001 for each treatment group before vs after treatment (Tukey's test.

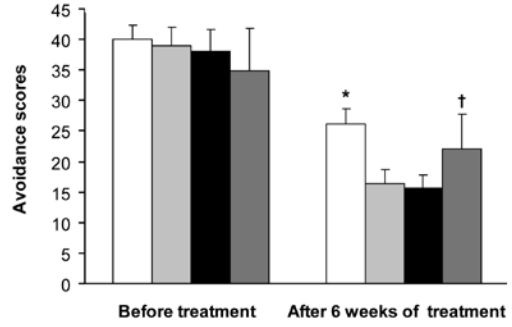

Figure 3. Avoidance scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with posttraumatic stress disorder. P<0.001 for each treatment group before vs after treatment. *P<0.001 vs the scores after 6 weeks of treatment with risperidone, olanzapine or quetiapine (Tukey's test). †P<0.001 vs the scores after 6 weeks of treatment with risperidone, or olanzapine (Tukey's test).

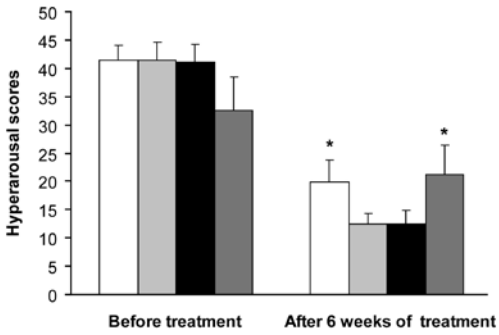

Figure 4. Hyperarousal scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder. *P*<0.001 for each treatment group before vs after treatment. **P*<0.001 vs the scores after 6 weeks of treatment with risperidone or olanzapine (Tukey's test).

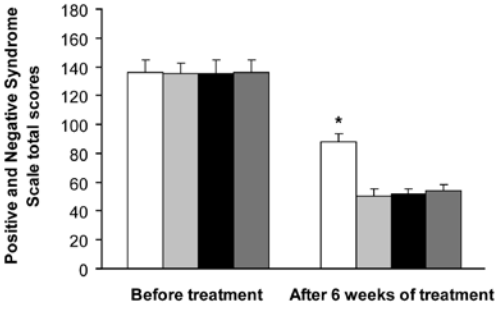

Figure 5. Positive and Negative Syndrome Scale total scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder. *P*<0.001 for each treatment group before vs after treatment. **P*<0.001 vs the scores after 6 weeks of treatment with risperidone, olanzapine or quetiapine (Tukey's test).

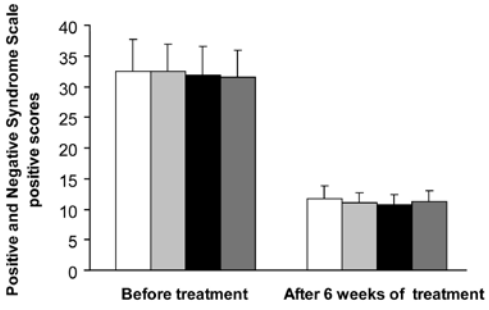

Figure 6. Positive and Negative Syndrome Scale positive scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder. *P*<0.001 for each treatment group before vs after treatment (Tukey's test).

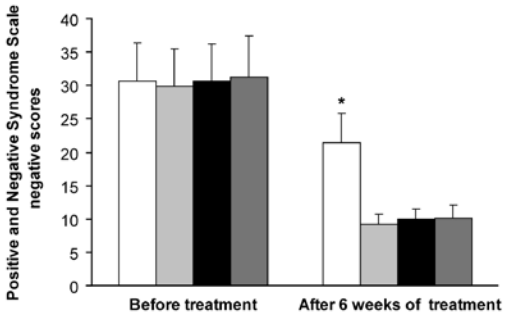

Figure 7. Positive and Negative Syndrome Scale negative scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder *P*<0.001 for each treatment group before vs after treatment. **P*<0.001 vs the scores after 6 weeks of treatment with risperidone, olanzapine or quetiapine (Tukey's test).

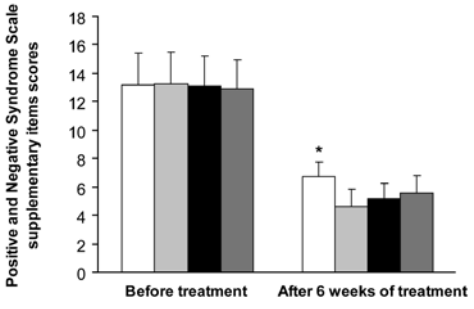

Figure 9. Positive and Negative Syndrome Scale supplementary items scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder. *P*<0.001 for each treatment group before vs after treatment. **P*<0.001 vs the scores after 6 weeks of treatment with risperidone or olanzapine (Tukey's test).

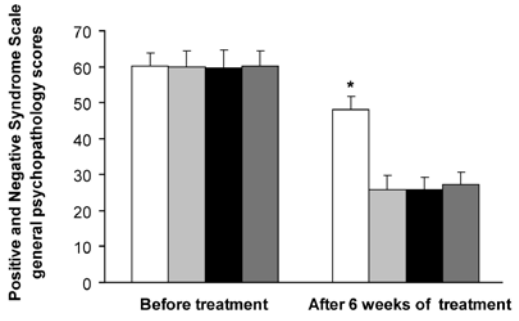

Figure 8. Positive and Negative Syndrome Scale general psychopathology scores (mean ± standard deviation) before and after 6 weeks of treatment with fluphenazine (open bars), olanzapine (light gray bars), risperidone (closed bars), or quetiapine (dark gray bars) in war veterans with psychotic combat-related posttraumatic stress disorder. *P*<0.001 for each treatment group before vs after treatment. **P*<0.001 vs the scores after 6 weeks of treatment with risperidone, olanzapine or quetiapine (Tukey's test).

er decrease of 35% in the baseline Positive and Negative Syndrome scale scores in war veterans with psychotic PTSD (Figure 5). Positive scores were comparably decreased after all antipsychotic treatment (Figure 6),whereas negative (Figure 7) and general psychopathology (Figure 8) scores were decreased substantially more after olanzapine, risperidone or quetiapine than after fluphenazine treatment. Supplementary items scores on the Positive and Negative Syndrome scale were equivalently decreased from the baseline values: by 65% after olanzapine or by 61% risperidone treatment. The reduction by 49% achieved after fluphenazine treatment was not significantly different from the decrease from baseline scores by 57% induced by quetiapine treatment (Figure 9).

The scores in Clinical Global Impression of Severity of Illness scale were significantly reduced by 30% and 38% from the baseline scores with fluphenazine and quetiapine treatment, respectively, and by 62% and 64% after olanzapine or risperidone treatment, respectively ($P<0.001$ for all, Tukey's test).

Drug-induced Extrapyramidal Symptoms Scale scores and Patient's Global Impression of Improvement scores significantly differed between fluphenazine-treated veterans and those treated with other atypical antipsychotic medications ($P<0.001$ Tukey's test). War veterans with psychotic PTSD treated with fluphenazine had more extrapyramidal side effects (akathisia, rigor, and mild agitation), and patients had the impression of the smaller improvement than those treated with olanzapine, risperidone, or quetiapine.

Discussion

We analyzed retrospectively the effects of four antipsychotic drugs – fluphenazine, olanzapine, risperidone, and quetiapine – from 3 open-label clinical trials (25,26,41), in a well-characterized large group of ethnically and racially uniform Caucasian male war veterans, matched for age, combat experience, social, and cultural background, with combat-related PTSD with psychotic features. All antipsychotic drugs significantly reduced PTSD and psychotic symptoms in treatment-resistant war veterans with combat-related psychotic PTSD, which is in accordance with previous findings (12,14,17,18,25,26,41). Although all patients improved significantly after antipsychotic treatment, fluphenazine, olanzapine, risperidone, and quetiapine differently affected particular PTSD and psychotic symptoms. Treatment with fluphenazine, olanzapine, risperidone, or quetiapine equivalently and significantly reduced most of the trauma re-experiencing symptoms, as well as positive psychotic symptoms of the Positive and Negative Syndrome Scale in treatment-resistant patients. On the other hand, clear differences were found in the effects of fluphenazine, olanzapine, risperidone, and quetiapine on the total PTSD symptom scores and total Positive and Negative Syndrome Scale scores, on the symptoms listed in avoidance and hyperarousal subscales, and in negative, general psychopathology, and supplementary items subscales. Treatment with olanzapine and risperidone decreased total PTSD symptoms, symptoms of avoidance, hyperarousal, and reduced anger and affective lability, listed in the Positive and Negative Syndrome Scale supplementary items. This reduction of the symptoms was significantly greater than the reduction induced by fluphenazine or quetiapine. The treatment with olanzapine, risperidone or quetiapine greatly reduced the total Positive and Negative Syndrome Scale scores and negative and general psychopathology symptoms. These psychotic symptoms were also reduced by fluphenazine treatment, but its effect was weaker. Since a clinical response in PTSD is achieved when Clinician-administered PTSD Scale scores drop by 30% compared with baseline scores (5), all drugs used in this study showed good therapeutic efficacy, and patients had a good therapeutic response.

The clinical trials with antipsychotics in PTSD deserve considerable attention, since a

modest or significant clinical improvement was reported after treatment with neuroleptics or atypical antipsychotics in PTSD (5,14) either in a series of case reports (22,42-46) or in civilian PTSD subjects (22,42,43,47). However, the effects of antipsychotic drugs are confounded since participants received antipsychotic medication as an adjunct therapy (27,44,48-51).

The neuroleptic drug fluphenazine significantly reduced psychotic and PTSD symptoms in our war veterans, as reported previously (25), but induced akathisia, rigor, or mild agitation, which were alleviated after treatment with biperidone. Our results are in agreement with previous studies that showed the thioridazine-induced significant improvement of the sleep disturbances and reduction of nightmares, flashbacks, and anxiety in patients with PTSD (52) or combat-related PTSD (53). However, our results did not show the lack of improvement in the effects of neuroleptics compared with non-neuroleptic drugs in the large groups of male combat-related PTSD patients at baseline and after 12 months (54), or the failure to improve the symptoms of PTSD (22).

The treatment with atypical antipsychotic drugs in PTSD includes the use of risperidone (26,44-49,51), olanzapine (25,27,42,43,55,56), or quetiapine (41,50,57-60). Our present and previous results have shown that all three atypical antipsychotics induced substantial clinical improvement in treatment-resistant war veterans with psychotic PTSD (25,26,41). The good efficacy of olanzapine has been confirmed by the clinical improvement or the reductions in the Clinician-administered PTSD Scale or Positive and Negative Syndrome Scale scores after 5-16 weeks of treatment, either given as a monotherapy (25,56) or as an adjunct to other existing medications, mainly antidepressants (27). In line with our data, the beneficial effects of quetiapine (41,50,57-59,61) or risperidone (26,44-49,51,60) in the treatment of PTSD were described. The clinical improvement induced by the treatment with risperidone in psychotic combat-related PTSD (26) was confirmed also by a double-blind study (49) and by a series of case reports (46,51). However, only a few studies used risperidone as monotherapy and verified clinical improvement in combat-related PTSD (26,51). Risperidone induced akathisia, psychomotor agitation, and rigor, and these side effects were alleviated with biperidone. Other minor side effects were sedation, anxiety, slightly increased appetite, and weight gain of up to 4 kg. The positive effects of quetiapine in the treatment of PTSD were described in a few case reports (57,62) and studies (50,58,59); however, these studies mostly added quetiapine to an existing medication (50,58). The effect of quetiapine on the core PTSD symptoms was weaker than the effects of olanzapine and risperidone, but the dose used was lower than the one usually administered in schizophrenia (63). War veterans in our study were severely ill patients, with psychotic combat-related PTSD, and our results are in line with the previous report showing that monotherapy with quetiapine significantly improved clinical symptoms of PTSD and psychosis in PTSD patients refractory to other treatments (41). Quetiapine induced only mild and transient sedation, which occurred during the first 2 weeks of treatment.

The common pharmacological strategy in the treatment of PTSD is to start with selective serotonin reuptake inhibitors (13,64), alone or in combination with benzodiazepines, mood stabilizers (65), including anticonvulsants (66), if necessary. However, atypical antipsychotic drugs (25-27,41-51,55-61) may be the drugs of choice in treatment-resistant combat-related PTSD with psychotic symptoms (8,9,11,14,17,20-26, 29,67). Our results showed that atypical antipsychotic drugs (olanzapine, risperidone or quetiapine) had good efficacy in the treatment of chronic combat-related psychotic PTSD. These beneficial effects agree with their reported efficacy in the treatment of refractory subgroups of schizophrenic patients (63,68) and other non-

psychotic patients, such as treatment-resistant depression (69), borderline personality disorder (70), or severe childhood conduct disorder and autism (71,72).

The limitations of this study are its open and retrospective design and the fact that the raters, therapists, and patients were not blind to the treatment they received. Its value lays in the well-characterized large group of ethnically and racially uniform male war veterans, matched for age, combat experience, social and cultural background, the fact that patients received a monotherapy, the comparison of four antipsychotic drugs in the treatment-resistant combat-related PTSD with psychotic features, and the fact that patients were treated in the same facility and by the same team, so the treatment factors were similar.

In conclusion, our study has confirmed that monotherapy with atypical antipsychotics has clear beneficial effects in the treatment of treatment-refractory war veterans with psychotic PTSD. These data corroborate the wide spectrum of efficacy of atypical antipsychotic drugs (69) and confirm the hypothesis that atypical antipsychotics may act on the common underlying pathologic mechanism that may contribute to "treatment resistance" across diagnostic groups and symptom domains (48,69). Psychotic symptoms commonly occur in combat-related PTSD and the use of antipsychotic medications seems to offer another approach to treat psychotic subtype of combat-related PTSD resistant to previous antidepressant treatment.

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