*Psychiatria Danubina, 2009; Vol. 21, No. 3, pp 411–414* *Conference paper*


# PHARMACOTHERAPY TREATMENT OF PTSD AND COMORBID DISORDERS

**Dragica Kozarić-Kovačić**

*Department of Psychiatry, Dubrava University Hospital, Referral Center for Stress-related Disorders of the Croatian Ministry of Health and Social Welfare, Regional Center for Psychotrauma, Zagreb, Croatia*

***SUMMARY***

*Comorbity is very high in posttraumatic stress disorder (PTSD) patients. PTSD is very often complicated with depressive disorder, substance abuse, other anxiety disorders, personality disorders, psychotic features, etc. There have been few pharmacotherapy studies in this complicated field. In the past few years the literature on pharmacotherapy treatment for PTSD and comorbidity has arisen. From empirical evidence (level A) exist three sertraline studies in PTSD comorbid with: 1) anxiety, 2) depression, and 3) anxiety and depression, and one risperidone study in PTSD comorbid with psychotic symptoms. From empirical evidence (level B) exist two disulfiram, naltrexone, and their combination studies in patients with PTSD comorbid with alcohol dependence and one paroxetine or bupropion versus cognitive behavioral therapy (CBT) versus community mental health referral study in PTSD women outpatients with major depressive disorder.*

*The results from our label trials in the Croatian war veterans with chronic PTSD comorbid with psychotic features treated with novel antipsychotics (olanzapine, risperidone, or quetiapine) are promising. In the future more rigorously designed, comparative studies are needed to determine the usefulness, efficacy, tolerability, and safety of particular psychopharmaceutical drugs in the treatment of this therapeutically and functionally challenging disorder, especially the trials from level A.*

***Key words:*** *pharmacotherapy - posttraumatic stress disorders - comorbidity*

* * * * *

## INTRODUCTION

The rate of comorbidity is especially high in posttraumatic stress disorder (PTSD). 80% of individuals with PTSD meet criteria for at least one of the psychiatric diagnosis (life-time rates) (Kessler et al. 2005, Kozarić-Kovačić & Kocijan-Hercigonja 2001). The most frequent diagnoses are: major depressive disorder, other anxiety disorders, substance abuse, somatization, personality disorders, and dissociative disorders.

There are also atypical clinical pictures of PTSD, as well as the difference in clinical presentation of symptoms. Some investigations show different subtypes of PTSD with depressive, psychotic, and panic features (Hamner & Gould 1998, Kozarić-Kovačić & Borovečki 2005).

There is a central paradox in the field of PTSD comorbidity. Comorbidity with PTSD is the norm, yet treatment outcome studies routinely exclude patients with significant comorbid conditions and fail to assess for them (Najavits et al. 2009).

## RESULTS OF CLINICAL STUDIES

Although the comorbidity is very high in PTSD patients, there have been few pharmacotherapy studies in this complicated field. Two general types of studies related to comorbid PTSD exist: 1. efficacy studies of standard PTSD treatments in patients having comorbid diagnoses and 2. adjunctive pharmacotherapy studies for the treatment specific comorbidity or symptoms in patients having PTSD.

## PHARMACOTHERAPY STUDIES

**I**. Empirical evidence (Level A) - means that the study meets criteria for that level, but it may be that missing a small element (e.g. treatment conditions, or not randomizing to therapists, or not reporting interrater assessments reliability).

A) Sertraline studies in PTSD comorbid with: 1) anxiety, 2) depression, and 3) anxiety and depression

a) Brady & Clary, 2003 investigated efficacy and tolerability of flexible dose of sertraline (50-200mg/day) in 12-weeks, multicentric, double-blind, randomized study in 395 civilian outpatients having PTSD only, PTSD comorbid with anxiety, PTSD comorbid with depression, and PTSD comorbid with anxiety and depression. The total severity score of the Clinician-Administered PTSD Scale-2 (CAPS-2) equal or higher from 50 at the baseline was required for inclusion the patients. Greater improvement was for the sertraline group in comparison to placebo group in PTSD symptoms for persons with PTSD and comorbid anxiety alone, or comorbid anxiety and depression. There was no difference in side effects burden between groups.

b) Brady et al. 2005 examined sertraline in 94 (51 men and 43 women) civilian persons having PTSD comorbid with alcohol dependence. Study was 12-weeks, double-blind, and controlled. Dose was fixed of 150 mg of sertraline or placebo. Persons received sertraline with early-onset PTSD and less severe alcohol dependence demonstrated greater improvement than the persons treated with placebo. Oppositely, the placebo group showed greater improvement in the individuals with severe alcohol dependence and later-onset of PTSD. It may be that exist subtypes of persons with PTSD comorbid with alcohol dependence who respond differently to sertraline.

c) Labbate et al. 2004 investigated the impact of comorbid anxiety or affective disorders in PTSD patients on outcomes in PTSD persons having comorbid alcohol dependence in a post hoc analysis of previous trial. In this analysis the patients were divided in the four groups: 1. without comorbid anxiety or depression, 2. comorbid depression, 3. comorbid anxiety, and 4. both comorbidity with anxiety and depression. Persons with comorbid anxiety showed improvement in alcohol use, but study may not have been enough powered for such analysis.

B) Risperidone in study PTSD comorbid with psychotic symptoms

a) Hamner et al. 2003 examined adjunctive risperidone in dose from 1 to 6 mg/day, average dose of 2.5 mg/day in a 5-weeks, randomized, placebo-controlled trial in 37 combat veterans treated in outpatients setting. They were treated also with antidepressant or other pharmacotherapy which dose was stable one month prior to the study. Furthermore, the Positive and Negative Syndrome Scale (PANSS) score was equal or higher than 60 at baseline. Schizophrenia, schizoaffective disorder, or other primary psychotic disorders were excluded. Risperidone induced greater reduction in psychotic symptoms accompanied with chronic PTSD but not overall PTSD symptoms in comparison to placebo. Limitations of this study are small sample size, short duration, and possible inadequate dosage.

**II**. Empirical evidence (Level B) - means it is good study with enough major methodological weaknesses; they have some sort of control condition.

A) Disulfiram, naltrexone, and their combination

a) Petrakis et al. 2005 examined the efficacy of disulfiram and naltrexone, or their combination in 254 outpatients with alcohol dependence and different comorbid disorders. Duration of study was 12-weeks and half of the individuals met criteria for PTSD. Patients were treated with open-label disulfiram and different psychotropic medications which they received two weeks before the trial. They received naltrexone or disulfiram in comparison to placebo. Craving was reduced in disulfiram group in comparison to naltrexone group. Naltrexone and disulfiram groups were superior to placebo. There was no benefit from disulfiram and naltrexone combination, depression was even greater over the time.

b) Same group performed a secondary analysis of the same data (Petrakis et al. 2006). They investigated naltrexone vs. disulfiram. Patients with PTSD receiving naltrexone had improvement in alcohol outcomes in comparison to placebo group, and PTSD patients treated with disulfiram had improvement in alcohol craving, total PTSD symptoms, and hyperarousal symptoms. PTSD re-experiencing symptoms were improved in naltrexone group, and the group treated with combination had more side effects.

B) Paroxetine or bupropion versus cognitive behavioral therapy (CBT) versus community mental health referral

a) Green et al. 2006 investigated 267 low-income women with major depressive disorder in an uncontrolled trial. One third of them had comorbid PTSD. They were randomized to: 1. CBT, 2. antidepressant (paroxetine or bupropion), or 3. community mental health referral. Depression improved in both groups on medication in same rates over time. After one year follow-up women with PTSD had more depression and lower physical functioning.

## OUR OPEN LABEL TRIALS IN CROATIAN WAR VETERANS WITH CHRONIC PTSD COMORBID WITH PSYCHOTIC FEATURES

We included 134 male war veterans with chronic PTSD with psychotic combat-related features resistant to the antidepressive therapy. Atypical antipsychotics (fluphenazine, olanzapine, risperidone, or quetiapine) were given as a monotherapy.

Study designs were: comparative, 6 weeks treatment with fluphenazine (N=27) in 5-10 mg/day dose range, or olanzapine (N=28) in 5-10 mg/day dose range, or risperidone (N=26) in 2-4 mg/day dose range, or quetiapine (N=53) in 25-400 mg/day.

The used drugs have different affinities for the neurotransmitter's receptors. Fluphenazine has high affinity for D2 and D1, and moderate affinity for H1 histaminergic receptors. Olanzapine has high affinity for the 5-HT2, dopamine types (D1 to D4), muscarines types (M1 to M5), and H1 receptors. Risperidone has affinity for the 5-HT2, 5-HT7, dopamine type D2, muscarines types (M1 to M5), α1 and α2 adrenergic receptors, and high 5-HT2/D2 ratio which is characteristic of the atypical antipsychotic profile. Quetiapine has high affinity for H1 receptors, moderate for alfa1 and alfa2 adrenergic receptors, opioid receptors, 5-HT1A, D1 receptors and higher affinity for 5-HT2 than D2 receptors.

Inclusion criteria were: 1. a patients with current and chronic PTSD, comorbid with psychotic symptoms, 2. a diagnosis was made using structured clinical interview (SCID) for DSM-IV disorders (American Psychiatric Association 1994), 3. an existence of current PTSD was assessed with CAPS scale. We excluded patients who had: any psychiatric disorder before the war, a major depressive disorder, a primary diagnosis of another psychiatric disorder (currently or within the previous three months), a serious concomitant medical condition, a clinically significant ECG or laboratory findings, a serious risk of suicide, a history of seizure or misuse of alcohol or drugs. The clinical picture of psychotic symptoms consisted of: 1. a schizophrenia-like symptoms characterized mostly by conceptual disorganization, delusions and suspiciousness/ persecution, 2. a psychotic depression-like symptoms: hallucinatory behavior, depressive psychotic accusations, depressive delusions, and 3. a mixed clinical picture: conceptual disturbances and disorganization, persecutive and depressive delusions, visual and auditory hallucinations.

Psychotic symptoms were scored on the PANSS at least 4 on: 1. a positive items: delusions, conceptual disorganization, hallucinatory behavior, suspiciousness/persecution, 2. a negative items: emotional withdrawal, and passive/apathetic social withdrawal, 3. a general psychopathology subscale: guilt feelings, depression, motor retardation, unusual thought content, disorientation, disturbance of volition, poor impulse control and active social avoidance, and 4. a supplementary subscale: anger and affective lability.

Distinction of psychotic subtype of PTSD was determined with the lack of correlations between the positive (PANSS) and trauma re-experiencing and/or hyperarousal symptoms (CAPS) and the lack of association between negative (PANSS) and avoidance symptoms (CAPS).

Veterans with combat related PTSD included in the study (receiving fluphenazine, olanzapine, risperidone, or quetiapine treatment) were similar in following items: age, duration of combat experience, and scores in all measurement instruments.

The main findings of the studies are: 1. olanzapine, fluphenazine (Pivac et al. 2004), risperidone (Kozarić-Kovačić et al. 2005), and quetiapine (Kozarić-Kovačić et al. 2007) (given as a monotherapy) were effective in reducing the PTSD and psychotic symptoms in patients with psychotic combat-related PTSD, 2. fluphenazine, olanzapine, risperidone, or quetiapine all decreased significantly, and in a similar manner, the symptoms listed in PANSS positive, and CAPS trauma re-experiencing subscales, 3. olanzapine, risperidone, and quetiapine were more effective in reducing the symptoms listed in: PANSS negative, general psychopathology and supplementary items subscales, CAPS avoidance and increased arousal subscales, and CGI-S, CGI-I, and PGI-I scores, 4. fluphenazine induced more extrapyramidal symptoms than olanzapine, risperidone, or quetiapine, 5. olanzapine, risperidone, and quetiapine demonstrated higher efficacy, greater treatment response, and patients improved much better than after fluphenazine, 6. olanzapine, risperidone, and quetiapine decreased the frequency and intensity of the intrusive thoughts and visual images, 7. olanzapine, risperidone, and quetiapine reduced depressive symptoms, decreased aggression, suicidality, and impulsivity, 8. olanzapine, risperidone, and quetiapine improved the symptoms of insomnia, nightmares, hypobulia, anhedonia, and increased the interest and pleasure in daily activities in PTSD patients.

## CONCLUSION

Although there is insufficiency of the studies related to PTSD and comorbidity, existing studies of PTSD and comorbidity are promising because they showed those patients respond to the standard psychopharmacological medication as the patients without comorbidity. In the future we need more trials from the level A.

More rigorously designed, comparative studies are needed to determine the usefulness, efficacy, tolerability, and safety of particular psychopharmaceutical drugs in the treatment of this therapeutically and functionally challenging disorder.

One group of medications is often not enough for the treatment of all the PTSD symptoms, especially in cases where PTSD is comorbid with depression, alcoholism, borderline personality disorder, or psychotic, panic, or other disorders. Irrespective of the different mechanisms of action of drugs used in the treatment of PTSD, the final goal is always the same – to reduce distress, reinforce the psychological defence system, and restore the functioning of the person. However, evidence from controlled clinical trials showing the effectiveness of pharmacotherapy in PTSD is still unsatisfactory.

## REFERENCES

1. *Brady KT, Clary CM: Affective and anxiety comorbidity in posttraumatic stress disorder treatment trials of sertraline. Compr Psychiatry 2003; 44:360-369.*
2. *Brady KT, Sonne S, Anton RF, Randall CL, Back SE, Simpson K: Sertraline in the treatment of co-occurring alcohol dependence and posttraumatic stress disorder. Alcohol Clin Exp Res 2005; 29:395-401.*
3. *Green BL, Krupnick JL, Chung J, Siddique J, Krause ED, Revick D et al:. Impact of PTSD comorbidity on one year outcomes in depression trial. J Clin Psychology 2006; 62(7):815-835.*
4. *Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW: Adjunctive risperidone treatment in post-traumatic stress disorder: A preliminary controlled trial on effects on comorbid psychotic symptoms. Int Clin Psychopharmacol 2003; 18:1-8.*
5. *Hamner MB, Gould PB: Plasma dopamine beta-hydroxylase activity in psychotic and non-psychotic post-traumatic stress disorder. Psychiatry Res 1998; 77:175-81.*
6. *Kessler- RC, Chiu WT, Demler O, Merikangas KR, Walters EE: Prevalence, severity, and comorbidity of 12-month DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:617-627.*
7. *Kozarić-Kovačić D, Borovečki A: Prevalence of psychotic comorbidity in combat-related post-traumatic stress disorder. Mil Med 2005; 170:223-6.*
8. *Kozarić-Kovačić D, Kocijan-Hercigonja D: Assessment of post-traumatic disorder and comorbidity. Mil Med 2001; 166:677-80.*
9. *Kozarić-Kovačić D, Pivac N, Mück-Šeler D, Rothbaum BO: Risperidone in psychotic combat related posttraumatic stress disorder: an open trial. J Clin Psychiatry 2005; 66:922-7.*
10. *Kozarić-Kovačić D, Pivac N: Quetiapine treatment in an open trial in combat related posttraumatic stress disorder with psychotic features. Int J Neuropsychopharmacology 2007;10:253-61.*
11. *Labbate LA, Sonne SC, Randall CL, Anton RF, Brady KT: Does comorbid anxiety and depression affect clinical outcomes in patients with posttraumatic stress disorder and alcohol use disorder. Compr Psychiatry 2004; 45:304-310.*
12. *Najavits ML, Ryngala D, Back ES, Bolton E, Mueser TK, Brady TK. Treatment of PTSD and comorbid disorders: In: Foa BE, Keane MT, Friedman JM, Cohen AL, eds. Effective treatments for PTSD-second edition. New York: The Guilford Press, 2009: p. 508-535.*
13. *Petrakis IL, Polling J, Levinson C, Nich C, Carroll K, Ralevski E et al: Naltrexone and disulfiram in patients with alcohol dependence and comorbid psychiatric disorders. Biol Psychiatry 2005; 57: 1128-1137.*
14. *Petrakis IL, Polling J, Levinson C, Nich C, Carroll K, Ralevski E et al: Naltrexone and disulfiram in patients with alcohol dependence and comorbid posttraumatic stress disorder. Biol Psychiatry 2006; 60: 777-783.*
15. *Pivac N, Kozarić-Kovačić D, Mück-Šeler D: Olanzapine versus fluphenazine in an open trial in patients with psychotic combat-related posttraumatic stress disorder. Psychopharmacology 2004; 175:451-6.*

*Correspondence:*

*Prof. Dragica Kozarić-Kovačić, MD, PHD*
*Department of Psychiatry, Dubrava University Hospital*
*Av. Gojka Šuška 6, 10000 Zagreb, Croatia*
*E-mail: dkozaric_kovacic@yahoo.com*