

Psychopharmacotherapy of Posttraumatic Stress Disorder

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

Posttraumatic stress disorder (PTSD) is a psychiatric disorder that develops after a psychological trauma usually caused by a situation perceived as deeply threatening to a person's life or integrity. Complex neurobiological changes triggered by such a traumatic and stressful experience may explain a wide range of PTSD symptoms and provide the rationale for psychopharmacological treatment. Selective serotonin-reuptake inhibitors make the first-line treatment of PTSD. Clinical experience has shown that they are more effective than noradrenalin-reuptake inhibitors or tricyclic antidepressants. Antipsychotic drugs, especially atypical ones, have been shown effective in PTSD patients with psychotic characteristics or refractoriness to other treatments. Mood stabilizers seem to reduce mostly autonomous overreactions to stress, whereas the evidence for effectiveness of monoamine oxidase inhibitors is largely inconclusive. Other groups of medications, such as serotonin agonists and antagonists, new antidepressants, dual inhibitors of serotonin- and noradrenalin-reuptake, anticonvulsants, and opiate antagonists are also sometimes used in PTSD treatment. However, as shown in the present review, most clinical studies performed to date to investigate the effectiveness of different psychopharmacological agents in the therapy of PTSD have serious limitations in terms of small sample size, lack of blinding and randomization, and small effect size. 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.

> **Correspondence to:**

Dragica Kozarić-Kovačić
Dubrava University Hospital
Referral Center For Stress-related Disorders of
the Croatian Ministry of Health and Social Welfare
Regional Center for Psychotrauma
Avenija Gojka Šuška 6
10 000 Zagreb, Croatia
dkozaric_kovacic@yahoo.com

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Posttraumatic stress disorder (PTSD) is an anxiety disorder that can develop after experiencing or witnessing a life-threatening event, such as accident, disaster, war trauma, violence or abuse (family, sexual, physical, and/or psychological), or any situation that seriously threatens the integrity of a person (1). The disorder, however, does not develop in every person exposed to traumatic experience. Stress results from an interaction between the mind and the body. The brain is the organ that determines reaction to stress as it decides on what is stressful and controls biological and physiological responses to stress (2). These responses vary from one person to another due to differences in their biological, genetic, environmental, and psychological characteristics, as well as their personal history (3,4).

Stress causes neuroanatomical and neurochemical changes in the brain (5,6). Early traumatic experience (eg, abuse or severe neglect in childhood) may affect the brain structures and functions so as to make a person vulnerable to negative stressful events and more prone to later development of PTSD or other anxiety-related disorders (5,7-10). A particular genetic profile also plays a role in vulnerability or resilience to stress (3,11). For example, individuals with a short *ss* allele of serotonin transporter are more vulnerable to depression (7) and PTSD (4), especially if they had early traumatic experience. A long-term dysregulation of cortisol and noradrenalin, the main stress mediators, favors the development of different anxiety disorders, including PTSD (12,13). Stress-induced changes in hippocampus (atrophy), amygdalae (volume reduction), and prefrontal cortex are also frequent findings in patients with these disorders (14-16).

The neurobiological changes in the brain, which result from dysregulation of noradrenergic (12), serotonergic (17,18), dopaminergic (19,20), and other neurotransmitter

systems, provide the basis for psychopharmacologic treatment of patients with PTSD (21,22).

Goals of PTSD pharmacotherapy

PTSD has two main groups of symptoms. The first group consists of core PTSD symptoms, which include persistent re-experiencing of traumatic event (flashbacks, nightmares), persistent avoidance of stimuli, hyperarousal, and withdrawal (1). The second group is comprised of secondary symptoms, which include impaired functioning, poor coping skills, and psychiatric comorbidity, which is present in around 80% of the cases (23,24). All these symptoms may be targeted in pharmacological treatment combined with psychosocial and psychotherapeutic support (25).

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 defense system, and restore the functioning of the person. However, evidence from controlled clinical trials showing the effectiveness of pharmacotherapy in PTSD is still unsatisfactory.

Pharmacotherapeutic studies in PTSD treatment

Given that PTSD has a wide range of symptoms resulting from dysregulation of several neurohormonal and neurochemical systems, many psychopharmacologic agents have been investigated for the treatment of PTSD either alone or comorbid with other conditions. Their use has been tested in controlled (Table 1) and

open (Table 2) clinical trials or reported in individual patients (Tables 1 and 2).

Selective serotonin-reuptake inhibitors

Selective serotonin-reuptake inhibitors (SSRI) are the first-choice treatment for PTSD and all

other anxiety disorders (103-105), despite the fact that only a few clinical trials investigating their effectiveness in this indication have been double-blind and controlled (most were open trials). The current attitude that serotoninergic medications are more effective than nor-

Table 1. Controlled clinical trials of psychopharmacologic agents used in the treatment of posttraumatic stress disorder, per medication group, in the order of publication*

Study, year (ref. No.)	No. of patients	Medication (daily dosage)	Study duration	Main findings
TCA				
Frank et al, 1988 (26)	62	imipramine†, phenelzine, placebo	8 weeks	Both medications, but especially phenelzine, improved IES score.
Reist et al, 1989 (27)	18	dezipramine (100-200 mg), placebo	4 weeks	No change in PTSD, depression reduced in dezipramine group.
Davidson et al, 1990 (28)	46	amitriptyline (50-300 mg), placebo	8 weeks	Significant improvement in HAMD score after completed 4 weeks; improvement on other measurement scales after completed 8 weeks of treatment.
Kosten et al, 1991 (29)	62	imipramine (50-300 mg), phenelzine (15-75 mg)placebo	8 weeks	Both medications superior to placebo.
Davidson et al, 1993 (30)	62	amitriptyline (50-300 mg), placebo	8 weeks	Reduced anxiety, depression, and IES scores in amitriptyline group.
MAOI/RIMA				
Shestatzky et al, 1988 (31)	13	phenelzine (45-75 mg), placebo	5 weeks	No difference.
Katz et al, 1994-1995 (32)	45	brofaromine (50-150 mg), placebo	14 weeks	Brofaromine significantly reduced PTSD symptoms.
Baker et al, 1995 (33)	118	brofaromine (up to 150 mg), placebo	12 weeks	No difference in CAPS score; brofaromine improved CGI score.
SSRI				
van der Kolk et al, 1994 (34)	64	fluoxetine (20-60 mg), placebo	5 weeks	Fluoxetine effective in PTSD treatment, which may be explained by inclusion of civilian patients.
Connor et al, 1999 (35)	53	fluoxetine (20-60 mg), placebo	12 weeks	Fluoxetine superior to placebo (civilian PTSD).
Hertzberg et al, 2000 (36)	12	fluoxetine (10-60 mg), placebo	12 weeks	No difference in comparison with placebo.
Brady et al, 2000 (37)	187	sertraline (50-200 mg), placebo	12 weeks	Sertraline superior to placebo.
Meltzer-Brody et al, 2000 (38)	53	Fluoxetine†, placebo		Significant changes in all groups of PTSD symptoms.
Martenyi et al, 2007	411	Fluoxetine (20-40 mg), placebo	12 weeks	No difference on CAPS scale in comparison with placebo.
Tucker et al, 2001 (39)	307	paroxetine (20-50 mg), placebo	12 weeks	CGI score improvement of 50% in paroxetine group and 43.5% in placebo group.
Marshall et al, 2001 (40)	365, 186	paroxetine (20-40 mg), placebo	12 weeks	CGI score improved in 63% and 57% of patients receiving paroxetine 20 mg and 40 mg, respectively, and in 37% of patients receiving placebo.
Davidson et al, 2001 (41)	100	sertraline (50-200 mg), placebo	12 weeks	Sertraline shown to be safe, well-tolerated, and effective treatment for PTSD.
Stein et al, 2003 (42)	307	paroxetine (20-50 mg), placebo	12 weeks	CGI score improved in 59% of patients receiving paroxetine and 39% of patients receiving placebo.
Antipsychotic agents				
Butterfield et al, 2001 (43)	15	olanzapine (5-20 mg), placebo	10 weeks	No difference.
Hamner et al, 2000 (44)	40	risperidone (1-6 mg), placebo	5 weeks	Significantly reduced PANSS score and symptoms of re-experiencing.
Stein et al, 2002 (45)	19	olanzapine†, placebo	12 weeks	Despite the small sample, olanzapine and other atypical antipsychotic agents relatively effective in PTSD refractory to SSRI therapy. Especially useful in reducing sleep problems.
Bartzokis et al, 2005 (46)	73	risperidone + psychotropic medications†, placebo	4 mo	Added risperidone improved many psychiatric symptoms in patients with chronic war-related PTSD.
Rothbaum et al, 2008 (47)	45 (phase 1) 25 (phase 2)	sertraline + risperidone†	8 weeks (each phase)	Sertraline – open study (phase 1). Risperidone with sertraline – placebo-controlled (phase 2).
Anticonvulsants				
Hertzberg et al, 1999 (48)	15	lamotrigine (25-500 mg), placebo	12 weeks	Lamotrigine may be effective as a primary psychopharmacologic treatment in war-related and civilian PTSD and as additional therapy to antidepressants in PTSD treatment.
Other medications				
Braun et al, 1990 (49)	16	alprazolam (2.5-6.0 mg), placebo	5 weeks	No changes in PTSD clinical picture.
Kaplan et al, 1996 (50)	13	inositol (12 g), placebo	4 weeks	No effect on PTSD.

*Abbreviations: PTSD – posttraumatic stress syndrome; TCA – tricyclic antidepressants; IES – Impact of Event Scale; HAMD – Hamilton Depression Scale; MAOI – monoamine oxidase inhibitors; RIMA – reversible inhibitor of monoamine oxidase (type A); SSRI – selective serotonin-reuptake inhibitors; CAPS – Clinician-Administered PTSD Scale, CGI – Clinical Global Impressions scale; PANSS – Positive and Negative Syndrome Scale.

†Dosage was not reported in the study.

Table 2. Open clinical trials of psychopharmacologic agents in the treatment of posttraumatic stress disorder, per medication group, in the order of publication*

Study, year (ref. No.)	No. of patients	Medication (daily dosage)	Study duration	Main findings
TCA				
Kinzie and Leung, 1989 (51)	9	imipramine (50-150 mg), clonidine (0.2-0.6 mg)	12-19 mo	Promising for depression and severe trauma treatment in patients with PTSD+MMD; slight influence on avoidance symptoms.
MAOI				
Lerer et al, 1987 (52)	23	phenelzine (30-90 mg)	4-18 weeks	Results partly confirm previous positive reports on PTSD treatment with phenelzine.
SSRI				
Davidson et al, 1991 (53)	5	fluoxetine (20-80 mg)	8-32 weeks	Significant improvement in intrusive and avoidance symptoms in patients with civilian trauma.
den Boer et al, 1991 (54)	24	fluvoxamine (300 mg)	12 weeks	Minimal improvement in intrusive symptoms and hyperarousal.
Shay, 1992 (55)	18	fluoxetine†		Reduced explosiveness, impulsiveness, and depression; additional therapy with trazodone often needed for insomnia; vomiting, diarrhea, and decreased libido as side effects.
Nagy et al, 1993 (56)	27	fluoxetine (20-80 mg)	10 weeks	Reduced re-experiencing of trauma and hyperarousal in patients with war-related PTSD.
Kline et al, 1994 (57)	19	sertraline (50-200 mg)	12 weeks	Symptoms reduced by 61% in all three PTSD groups of symptoms and reduced alcohol consumption in patients with PTSD and alcoholism.
Brady et al, 1995 (58)	9	sertraline (50-200 mg)	12 weeks	Could be effective in PTSD comorbid with alcoholism.
Marmar et al, 1996 (59)	10	fluvoxamine (100-250 mg)	10 weeks	Effective in reducing core PTSD symptoms in patients with war trauma.
Rothbaum et al, 1996 (60)	5	sertraline (75-150 mg)	12 weeks	CAPS score reduced by 53% in women with rape-related PTSD.
Davidson et al, 1998 (61)	15	fluvoxamine (50-200 mg)	8 weeks	Effectively reduced PTSD scores in 40%-50% of patients with civilian PTSD.
Marshall et al, 1998 (62)	13	paroxetine (10-60 mg)	12 weeks	Effectively reduced all three groups of PTSD symptoms and disassociative symptoms in patients with non-war-related PTSD.
Seedat et al, 2002 (63)	24 children 14 adults	citalopram (20-40 mg)	8 weeks	Effective in both age groups.
Robert et al, 2006 (64)	25	escitalopram (10 mg and 20 mg)	4 weeks 8 weeks	CAPS avoidance/numbing and CAPS hyperarousal subscale scores were decreased. HAMD and DTS also significantly improved.
Anticonvulsive agents				
Lipper et al, 1986 (65)	70	carbamazepine (400-1000 mg)	5 weeks	Improvement in intrusive symptoms, reduced nightmares and flashbacks in patients with war-related PTSD and substance abuse.
Wolf et al, 1988 (66)	10	carbamazepine (800-1200 mg)	unspecified	Improved impulse control in patients with war-related PTSD and substance abuse.
Fesler, 1991 (67)	16	valproic acid (250-2000 mg), various psychotropic agents	2-16 mo	General improvement of hyperarousal symptoms in patients with war-related PTSD.
Szymanski and Olympia, 1991 (68)	2	valproic acid†, TCA		
Looff et al, 1995 (69)	28	carbamazepine†		No symptoms after treatment in 22 of 28 children with PTSD and history of sexual abuse.
MacLeod, 1996 (70)	1	vigabatrin†		Beneficial response in a patient with PTSD.
Brannon et al, 2000 (71)	1	gabapentin†		Beneficial response in a patient with PTSD.
Antipsychotic agents				
Hamner, 1996 (72)	1	clozapine†		Beneficial effects in a patient with PTSD and comorbid psychosis.
Leyba, 1998 (73)	4	risperidone combined with other medications†		Case reports of 4 patients with PTSD.
Krashin and Oates, 1999 (74)	2	risperidone†		Case report on risperidone in the treatment of intrusive thoughts and consequent emotional reactivity in patients with PTSD.
Monelly and Ciraulo, 1999 (75)	1	risperidone (1 mg), paroxetine, diazepam†		Case report on risperidone in a patient with PTSD.
Labbate and Douglas, 2000 (76)	no data	olanzapine†		Greatest beneficial effect on sleep problems in patients with PTSD.
Hamner et al, 2001 (77)	20	additional quetiapine (25-300 mg)	6 weeks	Significant improvement in PANSS score, depression, and reexperiencing in patients with war-related PTSD.
Petty et al, 2001 (78)	48	olanzapine†	8 weeks	Useful in alleviating symptoms of war-related PTSD.
Tomić et al, 2001 (79)	71	clozapine (50 mg), zolpidem (10 mg)	7 d	Significant improvement in insomnia, CGI-S and PGI-S scores in patients receiving clozapine.
Filteau et al, 2003 (80)	5	quetiapine†		Reduced flashbacks in war-related and civilian PTSD.
Hamner et al, 2003 (81)	20	quetiapine (25-300 mg)	6 weeks	Quetiapine was well-tolerated and effective in reducing PTSD symptoms in patients refractory to other medications.

Table 2. Open clinical trials of psychopharmacologic agents in the treatment of posttraumatic stress disorder, per medication group, in the order of publication** (continued)

Study, year (ref. No.)	No. of patients	Medication (daily dosage)	Study duration	Main findings
Sokolski et al, 2003 (82)	68	additional quetiapine†		Useful in treatment of refractory PTSD symptoms in war veterans.
David et al, 2004 (83)	12	additional risperidone (1-3 mg)	12 weeks	Beneficial effects on re-experiencing trauma and psychotic symptoms in psychotic, agitated patients with PTSD.
Pivac et al, 2004 (84)	55	olanzapine (5-10 mg), fluphenazine (5-10 mg)	6 weeks	Significant improvement in PANSS score and Watson's trauma re-experiencing subscale in patients with war-related PTSD.
Kozarić-Kovačić et al, 2005 (85)	26	risperidone (2-4 mg)	6 weeks	Significant improvement in PANSS and CGI-S scores in war-related PTSD.
Kozarić-Kovačić et al, 2007 (86)	53	quetiapine (25-400 mg)	8 weeks	Significantly reduced PTSD and psychotic symptoms in patients with war-related PTSD.
Other medications				
Kitchner and Greenstein, 1985 (87)		lithium (300-600 mg)		Reduced anger and aggression and increased effects of concomitantly administered analgesics and anxiolytic agents.
Famularo et al, 1988 (88)	11	propranolol (0.8-2.5 mg/kg/d)	2 weeks	Significantly improved PTSD symptoms in children with acute trauma.
Brophy, 1991 (89)	2	cyproheptadine (16-24 mg)		Effective in insomnia and nightmares.
Bills and Kreisler, 1993 (90)	2	naltrexone		Improvement in flashbacks.
Glover, 1993 (91)	18	nalmefene†		Reduced frequency of flashbacks in several patients with PTSD.
Hargrave, 1993 (92)	1	trazodone (400 mg), buspirone (45 mg)	8 weeks	Effective in treatment of PTSD and disruptive behavior in a patient with dementia.
Duffy and Malloy, 1994 (93)	8	buspirone (5-30 mg)	4 weeks	Possible effective in patients with war trauma.
Fitchner and Crayton, 1994 (94)	10	buspirone (10-60 mg), different antipsychotic agents	12 mo	Response in 40% of war veterans with alcohol abuse in some cases.
Fortser et al, 1995 (95)	2	lithium (1200-1800 mg)		Reduced aggressive behavior in two war veterans with PTSD
Horrigan and Barnhill, 1996 (96)	1	guanfacine (1-2 mg)	6 weeks	Suppression of nightmares in a woman with PTSD related to sexual trauma.
Dow and Kline, 1997 (97)	72	12 antidepressants (2 SSRIs, 6 mo 6 TCA, 1 MAOI, trazodone, bupropione, lithium)		Superiority of SSRIs over noradrenergic antidepressants in patients with PTSD and comorbid MDD.
Hamner and Frueh, 1998 (98)	1	venlafaxine (150-225 mg)		Successful treatment in a war veteran resistant to several SSRIs, with a further improvement after the daily dosage increase.
Connor et al, 1999 (99)	6	mirtazapine (up to 45 mg)	8 weeks	Clinical improvement in 50% of patients with severe chronic PTSD, justifying further double-blind, placebo-controlled investigation, but with a small sample size and high comorbidity rate.
Davidson et al, 1998 (100)	17	nefazodone (50-600 mg)	12 weeks	Effectively reduced PTSD symptoms by 60% in patients with civilian trauma.
Hertzberg et al, 1998 (101)	10	nefazodone (100-600 mg)	12 weeks	Effective for all three groups of PTSD symptoms, including sleep disorder symptoms in patients with war trauma.
Hidalgo et al, 1999 (102)	105	nefazodone (up to 600 mg)		Results of 6 different open studies showed a wide spectrum of effects on PTSD symptoms.

*Abbreviations: PTSD – posttraumatic stress disorder; TCA – tricyclic antidepressants; MDD – major depressive disorder; SSRI – selective serotonin-reuptake inhibitors; CAPS – Clinician-Administered PTSD Scale; HAMD – Hamilton Depression Scale; DTS – Davidson Trauma Scale; MAOI – monoamine oxidase inhibitors; PANSS – Positive and Negative Syndrome Scale.

†Dosage not reported in the study.

adrenergic ones is mostly based on the clinical experience. The treatment with SSRI is recommended to last 6-8 weeks before the response evaluation. In case the treatment response is found unsatisfactory, psychiatric consultation or another antidepressant is recommended. However, if it is found satisfactory, the maintenance treatment is recommended to last 12 months.

Fluvoxamine. Fluvoxamine has been investigated in the treatment of PTSD in open trials with small patient samples (Table 2),

while double-blind, placebo-controlled studies are still lacking. Den Boer et al (54) administered fluvoxamine over 12 weeks in 24 World War II veterans and found minimal improvement in intrusive symptoms and arousal. Another study in 11 Vietnam War veterans found that fluvoxamine was well-tolerated and effective in reducing the core PTSD symptoms (59). In 15 civilians with PTSD who daily received 50-200 mg fluvoxamine over 8 weeks, PTSD symptoms were significantly reduced (61).

Fluoxetine. Fluoxetine has been evaluated in the treatment of PTSD in several controlled, open trials. A study performed in 5 non-veterans showed improvement in intrusive and avoidance symptoms after administration of fluoxetine over 8-32 weeks (53). Shay (55) treated 18 Vietnam War veterans with fluoxetine and observed reduction in explosiveness, impulsiveness, and depression. Another open prospective study in 19 patients with war-related PTSD showed a reduction in core PTSD symptoms after 10 weeks of fluoxetine treatment (56). A trial including 10 Vietnam War veterans found higher platelet paroxetine binding in patients with better response to fluoxetine treatment. These preliminary results imply that platelet paroxetine binding in PTSD patients could be used as a potential predictor of treatment response to SSRIs (105). Marteny et al (106) in a multicenter, double-blind, 12 weeks, placebo-controlled trial of 411 randomized PTSD patients, predominantly women found no difference between fluoxetine (20-40 mg) and placebo on CAPS scale. Placebo response rate in this study was higher than in previously published fluoxetine trials of PTSD (106). Van der Kolk et al (34) performed a double-blind placebo-controlled study among war veterans and non-veterans and found that fluoxetine significantly reduced PTSD core symptoms and depression after 5 weeks of treatment in non-veterans and veterans, respectively. In the study performed by Connor et al (35), 60 mg fluoxetine administered over 12 weeks reduced severe PTSD symptoms (especially intrusive thoughts and avoidance). On the other hand, Hertzberg et al (36) did not find any difference in symptom improvement between the patients receiving fluoxetine and those receiving placebo. Another study found that fluoxetine reduces the frequency of intrusive thoughts and avoidance symptoms, but not nightmares (38). These findings are similar to those of tricyclic anti-

depressants (TCA) and monoamine oxidase inhibitors (MAOI), which showed poorer results in the treatment of war-related than civilian PTSD.

Sertraline. The Food and Drug Agency approved sertraline for the treatment of PTSD in December 1999. In an open trial among 19 veterans with war-related PTSD, sertraline was shown to be relatively effective in reducing the symptoms of re-experiencing a traumatic event, hyperarousal, explosiveness, and depression (57). In another open trial in 9 patients with PTSD comorbid with alcoholism, sertraline was administered in the daily dosage of 50-200 mg over 12 weeks, producing 61% reduction in all three groups of PTSD symptoms and alcohol consumption (58). However, the patients in this trial also received psychotherapy and psychosocial treatment, which limits the interpretability of the results. Rothbaum et al (60) administered sertraline in 5 women with rape-related PTSD and found it relatively effective. In a double-blind, placebo-controlled, multicentric trial (37), sertraline was administered in flexible daily doses from 15 to 200 mg in 94 patients with PTSD, whereas placebo was administered in 73 patients. A significant improvement was found in 3 of 4 primary outcome measures (CGI-Severity of Illness scale, CGI-Improvement scale, and CAPS-II). Intensity of avoidance, withdrawal, and hyperarousal was reduced, but there was no observed effect on the symptoms related to re-experiencing traumatic events. Similar results were obtained by Davidson et al (41).

Paroxetine. In a 12-week open clinical trial in 17 civilian patients with chronic PTSD, paroxetine significantly reduced PTSD symptoms (62). Mean reduction of PTSD symptoms assessed by independent evaluators was 48%. Stein et al (42) analyzed three multicentric, placebo-controlled studies, which lasted 12 weeks each, applied almost identical meth-

odology, and included a large number of both male and female patients. In all three trials, there was a significant treatment response to paroxetine in all three groups of PTSD symptoms, ie, re-experiencing, avoidance, and hyperarousal, and CGI-Improvement Scale scores were improved in over 50% of the patients with PTSD (42). Furthermore, paroxetine in doses of 20 to 50 mg once a day has been shown effective in the treatment of chronic PTSD (improvement in all 3 symptom clusters) and associated with a significant reduction in disability after 12 weeks of treatment (39). In another study, paroxetine was administered in the dosage of 20 and 40 mg/d over 12 weeks and found effective and well-tolerated in adult patients with chronic PTSD (40).

Citalopram. There has been only one open clinical trial of citalopram in the treatment of PTSD in children and adult patients, which showed good efficacy of this medication in both age groups (63).

Escitalopram. It is an S-enantiomer of citalopram, which may have a faster onset and greater magnitude of effect than citalopram. Escitalopram was investigated in a preliminary open trial, the results of which suggested that escitalopram was both efficacious and well-tolerated in patients with PTSD (64).

Tricyclic antidepressants

Davidson et al (107) reviewed 7 placebo-controlled clinical trials evaluating different TCAs in the treatment of patients with civilian and war-related PTSD and found that the response was similar in both groups of patients, although slightly better in civilians.

There have been three double-blind clinical studies performed with TCA. A double-blind study with imipramine and phenelzine showed that both medications, especially phenelzine, improved PTSD symptoms on the Impact of Event Scale (26). Desipramine ad-

ministered over 4 weeks in 18 war veterans did not show any improvement (27); however, the period of administration was too short, which may explain the observed lack of effect, because later studies did show the drug to be effective in comparison with placebo. In a placebo-controlled study, amitriptyline administered in 46 veterans with chronic PTSD over 8 weeks improved HAMD score after 4 weeks, and other scores after 8 weeks (28). The improvement was less pronounced in cases with comorbid severe depression, panic disorder, and alcoholism. After the study was expanded to 62 subjects (30), poorer treatment response was found to be associated with higher levels of combat intensity, depression, neuroticism, anxiety, impaired concentration, physical symptoms, and feeling of guilt. Kosten et al (29) found that imipramine and phenelzine significantly reduced PTSD symptoms in comparison with placebo after 5 weeks, although imipramine was less effective than phenelzine (25% vs 44%) in reducing intrusive symptoms, but not symptoms of avoidance. This finding implies that imipramine is less effective than MAOI. Dow and Kline (97) investigated dezipramine and nortriptyline together with sertraline, fluoxetine, and phenelzine and found that the improvement of PTSD symptoms was more pronounced with sertraline and fluoxetine (SSRIs) than with the medications that mainly inhibited noradrenalin reuptake.

Dual inhibitors of serotonin- and noradrenalin-reuptake

Nefazodone. Only two of six open clinical studies investigating nefazodone in the treatment of PTSD in war veterans and traumatized civilians were published (100,101), whereas others were presented at conferences. Davidson et al (100) found significantly reduced PTSD symptoms, especially the symptoms of avoidance, in 17 patients with

civilian PTSD receiving nefazodone 600 mg a day over 12 weeks. The other study performed in 10 war veterans showed a 32% reduction in PTSD symptoms (101). Nefazodone was shown to influence a wide range of PTSD symptoms (102).

In a case report of Vietnam War veteran with PTSD resistant to several serotonergic medications, the treatment with 150 mg venlafaxine daily was successful, whereas further improvement was seen after the daily dosage was increased to 225 mg of venlafaxine (98).

Serotonin agonists and antagonists

Buspirone. Buspirone is a partial 5-HT_{1A} agonist, which was shown effective in the treatment of PTSD. The results of an open clinical trial in patients with chronic PTSD showed that buspirone reduced the PTSD core symptoms, namely, flashbacks, nightmares, and intrusive thoughts, as well as associated depressive and anxiety symptoms (93). Another study in 10 war veterans with PTSD treated with buspirone in combination with other psychotropic medications over one year found a poor treatment response (94).

Cyproheptadine. Cyproheptadine, 5-HT₂ serotonin antagonist, in a dosage of 4-28 mg a day was shown effective in reducing insomnia and nightmares in two war veterans (89).

Monoamine oxidase inhibitors

Phenelzine. Two double-blind clinical trials and one open clinical trial with phenelzine were performed in PTSD patients. Lerer et al (52) investigated effects of phenelzine administered over 4-18 weeks in an open clinical trial in 25 Israeli war veterans with PTSD. Thirteen of these veterans had a comorbid diagnosis (dysthymia, panic disorder, generalized anxiety disorder, or major depression). Although there was statistically significant improvement in some of the PTSD symptoms, the greatest beneficial effect was observed only on sleep

disturbance. Imipramine, phenelzine, and placebo were compared in a randomized, double-blind study, which included 62 veterans with PTSD and lasted 8 weeks (26). Although both medications were shown effective in comparison with placebo, the improvement was more pronounced with phenelzine than imipramine or placebo. CGI-Improvement Scale score showed improvement by 68% for phenelzine, 65% for imipramine, and 25% for placebo. On the Impact of Event Scale, the greatest reduction in symptoms was found for phenelzine (45%), followed by imipramine (25%) and placebo (5%). In another 5-week study in 13 patients with PTSD, there was no difference in improvement between phenelzine and placebo groups (31). The limitation of this study was a small sample size, short duration, and inhomogeneity with respect to the type of trauma.

Brofaromine. Katz et al (32) conducted a multicentric controlled trial of brofaromine combined with MAO-A and serotonin transporter inhibitor in 64 patients with non-war-related PTSD and found no differences between the drug and placebo, except in a subgroup of patients with chronic PTSD whose symptoms lasted more than a year and in whom the drug significantly reduced the PTSD symptoms. Another randomized, double-blind clinical trial in 146 patients with war-related PTSD did not show any difference between the brofaromine and placebo groups after 12 weeks, although both groups showed reduction in symptoms on the PTSD Clinical Scale (33). However, brofaromine has never been marketed and its role in PTSD treatment is not clear.

Other antidepressants

Connor et al (99) reported improvement of symptoms in 6 outpatients with severe, chronic PTSD who were treated with mirtazapine over 8 weeks; however, the validity of this pi-

lot study is very limited due to extremely low sample size and high comorbidity rate.

Tianeptine is recommended together with SSRIs as a first-line treatment for PTSD (108,109). Its positive effects are based on stimulation of neurogenesis, which was also observed with other antidepressants (110,111).

Adrenergic drugs

Different noradrenergic mechanisms can play a role in the pathophysiology of PTSD and typical PTSD-comorbid disorders, such as arousal disorders (anxiety, restlessness, insomnia, hypervigilance, and irritability) and memory disorders (112,113). Locus coeruleus is very rich in noradrenalin. Clonidine is an α -2 adrenergic agonist that decreases impulse activity of locus coeruleus neurons and inhibits noradrenergic activity by acting through pre-synaptic α -2 adrenoreceptors. It is used in the treatment of opiate withdrawal symptoms. Because of the observed similarity between opiate withdrawal symptoms and hyperactivity in PTSD patients, it has been used in the treatment of PTSD (114).

A study investigating noradrenergic antagonist propranolol and noradrenergic agonist clonidine showed a significant improvement in arousal and intrusion symptoms in war veterans with PTSD (115). In an open study combining imipramine and clonidine in refugees from Cambodia, improvement was observed in 6 patients, but with little effect on avoidance symptoms (51). Also, clonidine did not alleviate depressive symptoms, but when combined with imipramine, it was very effective in the treatment of major depression. Propranolol was effective in the treatment of reexperiencing and hyperarousal symptoms in an open clinical trial in 11 children with a history of sexual abuse (88).

Guanfacine, an α -2 agonist, improved sleep in PTSD patients with nightmares due to prolonged half-life of 18 to 22 hours (96).

Mood stabilizers

The rationale for administration of mood stabilizers in the treatment of PTSD is based on two assumptions. One is that affective instability is often present in PTSD patients and the other is that the kindling mechanism can cause stronger reactions to stress (116), which are also assumed to exist in bipolar disorders. Thus, medications against kindling could be effective in the treatment of PTSD (117).

Lithium. Only open clinical trials have been performed with lithium in the treatment of PTSD. Lithium administered in war veterans resistant to previous therapy over several weeks (serum levels between 0.2 and 0.4 $\mu\text{g/ml}$) reduced anger and aggression and increased the effects of concomitantly administered analgesics and anxiolytic drugs (87). Another study showed reduced autonomous arousal, stress reaction, and alcohol consumption in 14 of 22 patients treated with lithium (118). Forster et al (95) reported reduced aggressive behavior in two veterans with PTSD who were treated with 1200-1800 mg of lithium daily.

Carbamazepine. Two carbamazepine studies showed a significant improvement of symptoms in veterans with PTSD, irritability, and comorbid alcoholism (65,66; Table 2). One was performed in 10 patients in whom reduction of intrusive symptoms, flashbacks, and nightmares was reported after 5 weeks of carbamazepine treatment up to 1000 mg daily (65). In the other study, the dosage between 800 and 1000 mg daily was administered in 18 patients with uncontrolled behavior and head trauma without electroencephalographic changes (66). Loeff et al (69) reported impressive improvement in 28 children aged 8-17 years with history of sexual abuse who had PTSD symptoms associated with comorbid depression and deviant behavior. After the treat-

ment with clozapine, 22 of these children became symptom-free.

Valproic acid. There are two reports on the use of valproic acid in the treatment of patients with PTSD without comorbid depression. One is a study performed in 16 veterans with PTSD who were treated with valproic acid and other psychotropic agents, in which improvement in arousal symptoms was observed (67). The other is a case report of two patients with PTSD and intermittent explosive behavior, who self-reported improvement after treatment with valproic acid combined with TCA (68).

Lamotrigine. In a small double-blind, placebo-controlled trial, lamotrigine improved the symptoms of re-experiencing and avoidance (48).

Other anticonvulsants. A satisfactory treatment response in individual patients with PTSD was reported for gabapentin (71) and vigabatrin (70).

Antipsychotic medications

If administered as a monotherapy or in combination with other psychotropic drugs, atypical antipsychotic drugs seem to be effective in the treatment of PTSD refractory to other agents or combined with psychotic symptoms (119-121). They were also shown effective in reducing PTSD symptoms in Croatian war veterans with psychotic characteristics of either depressive or schizophrenic type (84-86).

Olanzapine. Olanzapine is an atypical antipsychotic medication shown to improve PTSD symptoms in patients with psychotic characteristics. In an open clinical trial, 28 patients with PTSD and psychotic characteristics resistant to previous therapy received olanzapine and 27 patients received fluphenazine over 6 weeks (84). Although both drugs were shown effective on the basis of the Positive and Negative Symptom Scale (PANSS) and Watson PTSD Scale scores, improvement was

more pronounced in patients taking olanzapine, who also had fewer extrapyramidal symptoms. Improvement was also found in another open study, in which olanzapine was administered alone (78), as well as when it was combined with antidepressants (45). Labate and Douglas (76) found that olanzapine improved sleep in patients with PTSD.

A randomized, placebo-controlled clinical trial in PTSD patients did not find olanzapine in the dosage of 5-20 mg to be effective (43).

Risperidone. Risperidone is another atypical antipsychotic drug administered in patients with PTSD and psychotic clinical picture. Open clinical trials were performed, showing a significant reduction in PTSD symptoms (46,47,73-75,83,85). Risperidone administered over 6 weeks was well-tolerated in 26 war veterans with psychotic PTSD, whose CAPS and PANSS score was reduced after only 3 weeks (85). Hamner et al (44) conducted a controlled clinical trial including 40 patients with chronic PTSD and chronic psychosis treated with risperidone combined with another therapy and found a significant reduction in PANSS score.

Quetiapine. Quetiapine has been evaluated only in open studies. It was found to reduce intrusive symptoms (77), flashbacks (80), and symptoms of re-experiencing traumatic events, avoidance, and arousal (81,82,122) in war veterans with chronic PTSD and psychotic symptoms refractory to other medications. In a study that lasted 8 weeks and included 53 war veterans with psychotic PTSD symptoms, quetiapine was administered as a monotherapy and produced a good treatment response in therapeutically-resistant patients (122).

Clozapine. Hamner (72) reported that clozapine had beneficial effects in a Vietnam War veteran with PTSD and comorbid paranoia, hallucinations, and thought disturbance. Clozapine was also effective in the treatment of

insomnia in patients with refractory PTSD or PTSD with psychotic elements (79).

Other medications

Opiate antagonists. Glover (91) showed that a long-acting opiate antagonist nalmefene reduced flashbacks in several PTSD patients by blocking internal opiate effect, which leads to emotional avoidance. Analgesia, which appears as a symptom in PTSD, can be internally induced and mediated by endogenous opiates. Chronic oversecretion of endogenous opiates in patients with PTSD manifests with a symptom of emotional avoidance, so often present in patients with PTSD (123). Bills and Kreisler (90) found that naltrexone reduced flashbacks in two PTSD patients.

Inositol. Inositol is a signal transduction modulator (second-messenger precursor), which showed humble effects in a small number of PTSD patients, in whom no significant difference was found in the improvement of symptoms in comparison with placebo (50).

Benzodiazepines. The administration of benzodiazepines is not recommended by the International Consensus Group on Depression and Anxiety due to their addictive potential (104), severe withdrawal symptoms (124), and little evidence of their effectiveness in the alleviation of PTSD symptoms (49,125). Moreover, many PTSD patients have a comorbid alcoholism, which additionally increases the risk of combined addiction (126).

Side effects

Side effects were inconsistently reported in the studies reviewed. In the study with fluoxetine, conducted by van der Kolk et al (34), the drop-out rate was very high and side effects were typical of an SSRI, ie, diarrhea, sweating, and headaches. In another study with fluoxetine, where additional administration of trazodone was used to treat insomnia, vomiting,

diarrhea, and decreased libido were reported (55). Rothbaum et al (60) administered sertraline in victims of rape; the medication was well-tolerated, although it was accompanied with side effects typical of SSRIs, like in the study by Davidson et al (58).

Side effects including vomiting, asthenia, sexual dysfunction, and sedation were mild and typical of SSRIs in three multicentric, placebo-controlled paroxetine studies (42). Daily doses of 20 mg and 40 mg of paroxetine were shown effective and were well-tolerated by adult patients with chronic PTSD who received the treatment over a 12-week period (40).

den Boer et al (54) performed a study with fluvoxamine where 11 subjects completed the trial, whereas 9 withdrew due to gastrointestinal side effects, sleep problems, and unspecified physical complaints.

Mild to moderate gastrointestinal disturbances were the most common adverse effects in a 12-week open-label study with escitalopram (64).

Anxiolytics (benzodiazepines) can cause severe withdrawal symptoms (124) because of the high risk for benzodiazepine abuse and dependence.

In a randomized controlled trial with risperidone for psychotic symptoms in patients with PTSD, only 2 patients withdrew from the trial and there were only minimal extrapyramidal symptoms (44). In another study (47), 5 participants withdrew due to adverse events that were possibly risperidone-related (tachycardia; increased liver enzyme – aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase; unremitting chest pain; and probable dystonic reaction). Another study showed that risperidone was generally well-tolerated with reported side effects consisting of akathisia, psychomotor agitation, rigor, sedation, and anxiety (85). Patients were administered biperiden to alleviate these ad-

verse effects (85). A comparative study of olanzapine vs fluphenazine in psychotic patients with combat-related PTSD showed that olanzapine was better tolerated than fluphenazine, which induced extrapyramidal side effects (akathisia, rigor, or mild agitation) that improved after biperidene (84). Quetiapine was well-tolerated with few reported side effects, such as mild and transient sedation (81,86).

PTSD and comorbidity

In PTSD, like in other psychiatric conditions, comorbidity is frequent (23,24). Given the complex etiology of PTSD due to involvement of multiple neurobiological mechanisms, comorbid conditions make the treatment more difficult. Many studies in PTSD treatment included patients with comorbid conditions, mostly depression (27,28,30,51,97,106), alcoholism and substance abuse (58,65,94), and psychotic symptoms (44-47,72,73,77,81-86).

In 2008, Mohamed and Rosenheck (127) identified all the medications taken by war veterans with PTSD over a one-year period to determine the extent of psychotropic medication use. They found that 80% of the patients received psychotropic medications. Of them, 89% were prescribed antidepressants, 61% anxiolytics or sedative-hypnotics, and 34% antipsychotics. Greater likelihood of medication use was associated with greater mental health service use and presence of comorbid psychiatric disorders. Medication-appropriate comorbid diagnoses were the most robust predictors of the use of each of the three groups of medications, ie, depressive disorders were associated with antidepressant use, anxiety disorders with anxiolytic or sedative-hypnotics use, and psychotic disorders with antipsychotic medications use. Thus, the authors concluded there was extensive use of diverse psychotropic medication classes in the treatment of PTSD in war veterans (127). While disease-specific use

of medications for both PTSD and comorbid disorders is common, a substantial number of prescribed medications seem to be unrelated to diagnosis and thus likely to be targeted at specific symptoms (eg, insomnia, anxiety, nightmares, or flashbacks) rather than diagnosed illnesses. A new type of efficacy research may be needed to determine symptom responses, as well as disorder responses, to psychotropic medications across different diagnoses.

Conclusion

Clinical trials, as well as clinical experience, have shown that psychopharmacological therapy has beneficial effects in most patients with PTSD. In addition to medications, PTSD patients should receive psychotherapy and social therapy. It is very important for the patient to adjust the lifestyle and decrease the exposure to stress in order to reduce chronic stress and development of associated diseases. Self-esteem and social support also contribute to the long-term health improvement and positive outcomes. The question of timing of the therapy, however, is still open. To prevent long-term consequences, intervention should follow immediately after trauma, because traumatic memory with time becomes resistant to therapy (128). On the other hand, early treatments are not always necessarily effective; in some cases, they have even been reported to aggravate the symptoms (129).

Most of the clinical trials presented in this article suffer from serious limitations due to small sample sizes, lack of blinding or randomization, and small effect size (130). For example, although SSRIs seem effective in the treatment of patients with PTSD symptoms, these open trials cannot be generalized and double-blind, placebo-controlled studies are needed to confirm their results (130). More rigorously designed, comparative studies should be performed to determine the usefulness, efficacy,

tolerability, and safety of particular psychoactive drugs in the treatment of this therapeutically and functionally challenging disorder.

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