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Review article

Pharmacologic alternatives to antidepressants in posttraumatic stress disorder: A systematic review

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ABSTRACT

The selective serotonin reuptake inhibitors (SSRIs) are considered the first-line pharmacological treatment for PTSD. However, even when treated with this class of drugs, response rates rarely exceed 60% and less than 20–30% of the patients achieve full remission. The aim of this study was to address this limitation by systematically reviewing the options left for the treatment of PTSD when patients do not respond satisfactorily to or tolerate SSRIs. A systematic review covering all original articles, letters and brief reports published in any language until October 2008 was conducted through searches in the ISI/Web of Science, PubMed and PILOTS databases. The search terms included the pharmacological class of each agent or its generic name plus "PTSD" or "stress disorder" in the title, in the abstract or as a keyword. Sixty-three articles were selected, covering the following categories: antipsychotics, anticonvulsants, adrenergic-inhibiting agents, opioid antagonists, benzodiazepines and other agents. None of the identified agents reached the level A of scientific evidence, 5 reached level B, 7 level C and 13 level D. The non-antidepressant agent with the strongest scientific evidence supporting its use in PTSD is risperidone, which can be envisaged as an effective add-on therapy when patients did not fully benefit from previous treatment with SSRIs. Prazosin, an adrenergic-inhibiting agent, is a promising alternative for cases of PTSD where nightmares and insomnia are prominent symptoms. So far, there is no consistent empirical support for using benzodiazepines in the prevention or in the treatment of PTSD, although these drugs could alleviate some associated non-specific symptoms, such as insomnia or anxiety. Further controlled clinical trials and meta-analysis are needed to guide clinicians in their search of effective pharmacological alternatives to antidepressants in PTSD.

Abbreviations: AP, Atypical Antipsychotics; b.i.d., *bis in die* or twice a day; BPRS, Brief Psychiatric Rating Scale; CAPS, Clinician Administered Posttraumatic Stress Disorder Scale; CGI, Clinical Global Impression; CGI-I, Clinical Global Impressions scale-Improvement item; CGI-S, Clinical Global Impressions-Severity of Illness Scale; CNS, Central Nervous System; CRF, Corticotropin Release Factor; DGRP, Physician Administered Duke Global Rating for PTSD Scale; DHEA, Dehydroepiandrosterone; DHEA-S, dehydroepiandrosterone sulfate; DTS, Davidson Trauma Scale; ER, Extended Release; FDA, Food and Drug Administration; GABA, Gamma-Aminobutyric Acid; IES-R, Impact of Event Scale-Revised; mg, Milligram; mg/kg/day, Milligram per Kilogram per Day; ng/ml, Nanograms per Millilitre; PANSS, The Positive and Negative Symptoms Scale; PCL-C, Posttraumatic Checklist-Civilian Version; PGI-I, Patient Global Impression-Improvement scale; PSS-SR, Posttraumatic Stress Disorder Symptoms Scale-Self Report; PTSD, Posttraumatic Stress Disorder; PTSD-I, Posttraumatic Stress Disorder Interview; PSQI, Pittsburgh Sleep Quality Index; RCTs, Randomized Clinical Trials; REM, Rapid Eye Movement; SCL-90R, Symptom Checklist-90 Revised; SNRI, Serotonin-norepinephrine Reuptake Inhibitor; SPRINT, Short PTSD Rating Interview; SSRIs, Selective Serotonin Reuptake Inhibitors; TOP-8, Treatment Outcomes PTSD Scale; TSCC, Traumatic Symptom Checklist in Children; VAMC, Miami Veterans Administration Medical Center.

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Contents

1. Introduction

Posttraumatic stress disorder (PTSD) is a pathological response to a traumatic event that is characterized by the presence of three clusters of symptoms: reexperiencing (cluster B), avoidance/numbing (cluster C), and hyperarousal (cluster D). The symptoms must last for a minimum of one month and disrupt functioning. If the symptoms persist for more than three months, then PTSD is considered to be chronic (American Psychiatric Association, 1994).

The treatment of PTSD has several specific goals: to reduce the severity of symptoms, to prevent and/or treat comorbid disorders, to decrease functional impairment, to modify pathogenic fear schemas, to prevent relapse, to build resilience and to improve quality of life (Ursano et al., 2004). The most common definitions of treatment response in PTSD patients are a decrease of 30% or more (Hamner et al., 2004) in the *Clinician Administered PTSD Scale* (CAPS) score (Blake et al., 1990) or a score of 1 ("very much") or 2 ("much improved") (Stein et al., 2006) in the Clinical Global Impressions scale-Improvement item (CGI-I) (Guy, 1976).

The selective serotonin reuptake inhibitors (SSRIs), especially paroxetine and sertraline, are considered the first-line pharmacotherapeutic treatment for PTSD (Schoenfeld et al., 2004; Ursano et al., 2004; Asnis et al., 2004). However, even when treated with this class of drugs, response rates rarely exceed 60% and less than 20–30% of the patients achieve full remission (Stein et al., 2002; Zohar et al., 2002). A 6-month long double-blind, placebo-controlled study conducted by Davidson et al. (2006) found that 78% of PTSD patients treated with the serotonin-norepinephrine reuptake inhibitor (SNRI) venlafaxine ER presented a positive clinical response (a decrease of ≥30% in the CAPS scores) but, nevertheless, only 40.4% of the completers achieved remission (CAPS score ≤20). Furthermore, treatment with venlafaxine ER failed to significantly ameliorate hyperarousal symptoms. Even considering the SSRIs, the most studied class of drugs, only two studies were able to demonstrate the superiority of paroxetine over placebo on all the three clusters of PTSD (Ballenger, 2004; Tucker et al., 2001). These findings may reflect an intrinsic limitation of SSRIs or SNRIs in ameliorating the heterogeneous symptoms of PTSD (Davidson et al., 2006). In spite of that, there are relatively few studies concerned with orienting clinicians about the benefits of combining or switching medications to manage patients with PTSD who did not respond adequately to first-line treatments (Kinrys et al., 2006).

The aim of this study was to address this limitation by systematically reviewing the therapeutic options left for the treatment of PTSD when patients do not respond satisfactorily to or tolerate SSRIs and SNRIs. This review will focus on the following categories of pharmacological agents: antipsychotics, anticonvulsants, adrenergic-inhibiting agents, opioid antagonists, benzodiazepines and other medications.

2. Methods

A systematic review covering all original articles, letters and brief reports published in any language until October 2008 was conducted through searches in the ISI/Web of Science, PubMed and PILOTS databases. The search terms included the pharmacological class of each agent (e.g. anticonvulsant*, or alpha-antagonist*) or its generic name (e.g. topiramate) plus "PTSD" or "stress disorder" in the title, in the abstract or as a keyword. The reference lists of retrieved articles were further scanned for additional relevant papers. Duplicate articles, reports on the efficacy of antidepressants in PTSD or case reports with less than five patients were preliminarily excluded. Whenever the authors of the present review had doubts about the methods or the results described in an article (i.e. if the drug was used as monotherapy), an e-mail was sent to the investigators requesting a clarification on the issue.

3. Results

One thousand, five hundred and eighty-three articles, letters and notes were identified: 404 on antipsychotics, 285 on anticonvulsants, 390 on adrenergic-inhibiting agents, 69 on opioid antagonists, 234 on

benzodiazepines, and on 201 other agents. After applying the exclusion criteria, sixty-three articles were selected and categorized according to the methodology, design, level of scientific evidence and clinical relevance (US Department of Health an Human Services, 1993), as follows:

A Multiple double-blind placebo-controlled trials with *positive* results and a confirmatory metanalysis (in addition to level B of evidence).
B At least one double-blind placebo-controlled trial with *positive* results (in addition to level C of evidence).
C Anecdotal reports, case series and open trials with *positive* results, in addition to expert endorsement or consensus.
D Few case reports with *positive* results, however without any expert panel endorsement.

The fully worked out results of our search are depicted in Table 1. Considering the critical relevance of the randomized clinical trials (RCTs) for the advancement of scientific knowledge in clinical psychopharmacology, the main characteristics (type of drugs, sample size, duration of the study, instruments employed, etc) of each of the available RCTs are featured in Table 2. Studies using less accurate methods, such as case reports and open trials were briefly summarized in the text below.

3.1. Antipsychotics

Although antipsychotics were not originally developed for the treatment of anxiety disorders, they are supposed to ameliorate PTSD symptoms through several mechanisms. Atypical antipsychotics (APs) act on serotonergic and dopaminergic systems, both of which have been implicated in the pathogenesis of PTSD (Eidelman et al., 2000; Hamner et al., 2003a). Some APs also show affinity for alpha-adrenergic receptors (Richelson, 1996), which have been demonstrated to be dysregulated in PTSD (Nutt, 2000; Raskind et al., 2000). In addition, due to antihistaminic effects, APs may alleviate insomnia and other sleep-related PTSD symptoms. Finally, some authors suggest that APs can reduce the cognitive and perceptual distortions in cases of PTSD with psychotic features (Butler et al., 1996).

3.1.1. Level of evidence B

3.1.1.1. Risperidone

3.1.1.1.1. Randomized clinical trials. Out of the six RCTs that have investigated the efficacy of risperidone in PTSD, only Padala et al.'s (2006) study has demonstrated its superiority over placebo as a monotherapy. Three RCTs also showed that risperidone as an adjunctive treatment was superior to placebo in decreasing the severity of PTSD symptoms (Bartzokis et al., 2005; Monnelly et al., 2003; Reich et al., 2004). None of these studies, however, found risperidone to be efficacious in alleviating avoidant behavior or emotional numbness. Hamner and colleagues failed to demonstrate any advantage of risperidone over placebo as an adjunctive therapy. It must be noted, nonetheless, that their findings were based on a short trial (5 weeks) conducted in a relatively small sample of war veterans (N=37) suffering from PTSD with psychotic symptoms (Hamner et al., 2003b). Similarly, Rothbaum et al. (2008) did not find any substantial differences among 20 civilian patients with refractory PTSD who received placebo or risperidone for 8 weeks as an adjunctive therapy after a 8-week open trial with sertraline, with only the insomnia being significantly alleviated in the risperidone-treated group.

3.1.1.1.2. Open label studies. Kozaric-Kovacic et al. (2005) treated 26 war veterans with refractory chronic PTSD and psychotic symptoms with risperidone (1–4 mg/day) as a monotherapy for 6 weeks. The *Positive and Negative Symptoms Scale* (PANSS) (Kay et al., 1987), the *PTSD Interview* (PTSD-I) (Watson et al., 1991), and the *Clinical Global Impressions-Severity of Illness Scale* (CGI-S) (Guy, 1976) were administered at baseline, third week and endpoint. All outcome measures and respective subscales showed significant decrease (p<0.05) from baseline to the third week of treatment; however, no further improvement was observed thereafter.

A 12-week open label study carried out by David et al. (2004) investigated the efficacy of risperidone (mean: 2.3 mg/day) as adjunctive therapy in 17 war veterans with refractory PTSD. The primary outcome measures were the CAPS (Blake et al., 1990) and the PANSS scores. Following treatment initiation, a significant decrease in PANSS total scores (p=0.002) and in each of its subscales was observed. CAPS total scores were also reduced (p=0.03) as were all CAPS subscales, except for the avoidant behavior/emotional numbness one. A secondary analysis conducted by the same group (David et al., 2006) demonstrated that risperidone was also efficacious as a adjunctive therapy for the treatment of the awakenings caused by trauma-related nightmares.

3.1.1.2. Olanzapine

3.1.1.2.1. Randomized clinical trials. We identified two RCTs with conflicting results (Table 2). Butterfield et al. (2001) employed the *Treatment Outcomes PTSD Scale* (TOP-8) (Connor and Davidson, 1999) and the *Short PTSD Rating Interview* (SPRINT) (Connor and Davidson, 2001) as outcome measures to assess the efficacy of olanzapine monotherapy in non-combat-related PTSD, but did not find it to be superior to placebo. Stein et al. (2002) compared the efficacy of adjunctive olanzapine and placebo in an 8-week trial with traumatized war veterans and found a significant decrease in the CAPS mean total scores with active medication. Patients who received olanzapine also showed significant improvement in sleep patterns. There were, however, no differences between the two groups in the *Clinical Global Impression* (CGI) final scores.

3.1.1.2.2. Open label studies. In a 6-week open label trial, Pivac et al. (2004) compared the efficacy of olanzapine monotherapy (5–10 mg/day, n=28) with that of fluphenazine (n=27) in patients suffering from chronic, refractory combat-related PTSD. Treatment with either drug was associated with significant reductions on weeks 3 and 6 in the scores of the PTSD-I subscales of reexperiencing, avoidant behavior, and autonomic arousal (p<0.001), in the scores of all subscales of the PANSS, and in CGI-S scores (p<0.05). The authors pointed out, however, that after 3 and 6 weeks of treatment the effects of olanzapine were superior to those of fluphenazine (p<0.05) in the avoidant and autonomic arousal subscales of the PTSD-I, in some specific PANSS subscales (negative symptoms, general psychopathology, and supplemental items), and in the CGI-S scores.

Petty et al. (2001) treated 48 PTSD combat veterans with olanzapine for 8 weeks and found a significant reduction in total scores of the CAPS and in the CGI.

3.1.1.2.3. Anecdotal reports and case series. Two case series (Jakovljevic et al., 2003; States and St.Dennis, 2003) reported a quick improvement of insomnia and nightmares in patients with civilian and combat-related refractory PTSD after the adding of olanzapine (2.5–20 mg/day) to their therapeutic schemes.

3.1.2. Level of evidence C

3.1.2.1. Quetiapine

3.1.2.1.1. Open label studies. In a 6-week open label study, Hamner et al. (2003a) evaluated the efficacy of quetiapine (25–300 mg/day) as an adjunctive therapy on 18 patients suffering from refractory combat-related PTSD. As early as the second week of treatment, a statistically significant reduction on the mean total scores of the CAPS-2 (Blake et al., 1990) (p<0.002) was observed which became more pronounced by the end of the study (p<0.0005). All PTSD symptom clusters improved, especially the B one. In a secondary analysis carried out by the same group (Robert et al., 2005), quetiapine was found to increase sleep quality and duration, while reducing vivid dreams and nightmares.

Table 1
Number of articles with non-antidepressant agents on the treatment of PTSD classified according to its experimental design and evidence level

Drug	RCTs	Open-label studies	Case reports and series	Total	Evidence level
Atypical antipsychotics					
Risperidone	6	3	0	9	B
Olanzapine	2	2	2	6	B
Quetiapine	0	4	1	5	C
Clozapine	0	1	0	1	D
Aripiprazole	0	0	1	1	D
Anticonvulsants					
Valproic acid	2	5	0	7	B
Lamotrigine	1	0	0	1	B
Topiramate	2	2	0	4	C
Tiagabine	1	1	0	2	C
Carbamazepine	0	3	0	3	C
Levetiracetam	0	1	0	1	C
Phenytoin	0	1	0	1	C
Gabapentin	0	0	1	1	D
Vigabatrin	0	0	1	1	D
Adrenergic-inhibiting agents					
Prazosin	3	3	2	8	B
Propranolol	0	2	0	2	C
Guanfacin	1	0	0	1	D
Clonidine	0	1	0	1	D
Opioid antagonists					
Nalmefene	0	1	0	1	D
Naltrexone	0	1	0	1	D
Benzodiazepines					
Alprazolam	1	1	0	2	D
Temazepam	0	1	0	1	D
Others					
Cyproheptadine	0	1	0	1	D
Dehydroepiandrosterone	0	1	0	1	D
Lithium	0	1	0	1	D

RCTs: randomized clinical trials.
Evidence level: B) At least one positive randomized clinical trial (in addition to level C evidence); C) Positive open trials, anecdotal evidence and case series, as well as endorsement by some experts; D) Positive anecdotal reports but not highly endorsed by expert panels.

Ahearn et al. (2006) investigated the efficacy of quetiapine (mean: 216 mg/day) as an adjunctive treatment in 15 civilian and veteran patients with refractory PTSD. After eight weeks of treatment, significant decreases were seen in the CAPS global (42%) and symptoms clusters scores. Significant reductions were also noted in the scores of the *Davidson Trauma Scale* (DTS) (Davidson et al., 1997) (45%) and of the *Sheehan Disability Scale* (Leon et al., 1992) (44%), a scale that assesses functional impairment.

Stathis et al. (2005) treated with quetiapine monotherapy (50–200 mg/day) six juveniles suffering from PTSD and living in a youth detention center. After six weeks, a significant reduction in the scores of the *Traumatic Symptom Checklist in Children* (TSCC) (Briere, 1996) was observed ($p<0.01$). Quetiapine was found to be particularly effective in the treatment of sleep problems, dissociative symptoms, anxiety, depression, and anger.

3.1.2.1.2. Anecdotal reports and case series. Filteau et al. (2003) reported that the use of quetiapine (150–200 mg/day) as an adjunctive treatment in 5 patients with refractory PTSD (3 due to combat situations and 2 resulting from rape) led to a marked reduction in the flashbacks. All patients had been treated previously with venlafaxine or with an SSRI in association with either gabapentin or lamotrigine but with unsatisfactory results.

3.1.3. Level of evidence D

3.1.3.1. Clozapine

3.1.3.1.1. Open label studies. Wheatley et al. (2004) used clozapine (600–800 mg/day) as a monotherapy to treat 6 teenagers involuntarily committed to a forensic hospital. All patients suffered from chronic PTSD with psychotic features resulting from sexual abuse. Three patients had comorbid schizoaffective disorder and two major depression. Although no specific instruments were employed to assess PTSD, a marked improvement was found when the *Brief Psychiatric Rating Scale* (BPRS) (Overall and Gorham, 1988) scores obtained during the six-month period following the treatment with clozapine were compared to those of the six-month period preceding it; aggressiveness and self-mutilatory behavior also decreased significantly.

3.1.3.2. Aripiprazole

3.1.3.2.1. Anecdotal reports and case series. Lambert (2006) treated five war veterans with PTSD with aripiprazole (15–30 mg/day) as an augmentation strategy. Four of them reported improved sleep patterns and reduced frequency of nightmares, while the last one experienced worsening of these symptoms.

3.2. Anticonvulsants

The phenomenon of kindling (repeated subthreshold stimulation of regions of the central nervous system making the neurons more reactive to low-intensity stimuli) has been demonstrated in limbic regions, including the amygdala (Cullen and Goddard, 1975), a structure that is linked to emotions like fear and to reactions to stress (Albucher and Liberzon, 2002). Given the well-known anti-kindling properties of the anticonvulsants (Iancu et al., 2002), it would be reasonable to presume that they might turn out to be useful in the treatment of PTSD.

Some anticonvulsants, like valproate, enhance GABAergic and serotonergic neurotransmission, and could be expected to be effective in the treatment of anxiety, depression, hyperarousal, and intrusive thoughts (Otte et al., 2004). Others, like lamotrigine, which inhibits glutamatergic neurotransmission, have been shown to have antidepressant properties in bipolar depression (Jefferson, 2005; Schaffer et al., 2006). Finally, valproate and carbamazepine have been demonstrated to be useful in the treatment of some of the most disturbing symptoms associated with PTSD, like increased irritability and aggressiveness.

3.2.1. Level of evidence B

3.2.1.1. Valproic acid

3.2.1.1.1. Randomized clinical trials. In the only RCT found comparing the efficacy of divalproex as a monotherapy (mean: 2309 mg/day) with placebo, Davis et al. (2008) treated 82 veterans suffering from PTSD for 8 weeks, but did not find any significant difference between the groups, as assessed by four difference outcome measures.

In a study by Steiner et al. (2007), 12 male youth with PTSD and conduct disorder involuntarily committed to the California Youth Authority were blindly randomized to receive, after a one-week washout period, either a high (between 500 and 1500 mg/day) or a low dose (up to 250 mg/day) of divalproex sodium monotherapy for seven weeks. At the end of the study, 88% of the subjects medicated with high doses were rated (using the CGI) as markedly improved as against none of those on the low-dose scheme ($p<0.016$). Given that this study did not include a control group treated with placebo it was not included in Table 2.

3.2.1.1.2. Open label studies. Fesler (1991) medicated 16 war veterans with PTSD with adjunctive valproate for 2 to 17 months (average: 13.6 months). Ten patients (62.5%) reported marked improvement, particularly in symptoms of hyperarousal and, to a lesser degree, of avoidance.

Clark et al. (1999b) administered divalproex, either as monotherapy (5 patients) or as an adjunctive treatment (11 patients) (1000–2500 mg/day; mean: 1365 mg/day), to combat veterans with PTSD. After 8 weeks, eleven (84.6%) patients had CGI scores of 1 (markedly improved) or 2 (much improved). The CAPS sub-scores revealed a more substantial improvement in the reexperiencing and in the hyperarousal domains.

Petty et al. (2002) treated 14 war veterans with PTSD with valproate as a monotherapy (1000–2500 mg/day; mean: 1850 mg/day) for

Table 2
Summary of randomized controlled trials for pharmacologic alternatives to antidepressants for treatment of PTSD

Study (year)	Sample (*N*)	Drug (mg/day)	Monotherapy/augmentation	Duration (weeks)	Outcome measures	Was active drug superior to placebo? (*p*-value)[a]			
						Symptoms of PTSD	Cluster B	Cluster C	Cluster D
Atypical antipsychotics									
Bartzokis et al. (2005)	Veterans (65)	Risperidone (1 to 3)	Augmentation	16	CAPS	Yes (<.05)	No	No	Yes (<.01)
Hamner et al. (2003a,b)	Veterans (37)	Risperidone (1 to 6)	Augmentation	5	CAPS	No	No	No	No
Reich et al. (2004)	Civilians (21)	Risperidone (0.5 to 8)	Augmentation	8	CAPS	No	No	No	No
					CAPS-2	Yes (.015)	Yes (<.001)	No	Yes (.006)
Padala et al. (2006)	Civilians (20)	Risperidone (1 to 6)	Monotherapy	12	CAPS	Yes (.04)	NR	NR	NR
					TOP-8	Yes (.028)	NR	NR	NR
Rothbaum et al. (2008)	Civilians (20)	Risperidone (mean: 2.1)	Augmentation	8	CAPS	No	NR	NR	NR
					CGI	No	NR	NR	NR
					DTS	No	Yes, insomnia (.03)	NR	NR
Monnelly et al. (2003)	Veterans (15)	Risperidone (0.5 to 2)	Augmentation	6	PCL-M	Yes (.02)	Yes (.001)	No	No
Stein et al. (2002)	Veterans (19)	Olanzapine (10 to 20)	Augmentation	8	CAPS	Yes (>.05)	NR	NR	NR
					CGI	No	NR	NR	NR
					PSQI (nightmares)	NA	Yes (.01)	NA	NA
Butterfield et al. (2001)	Civilians (15)	Olanzapine (5 to 20)	Monotherapy	10	TOP-8	No	No	No	No
					SPRINT	No	No	No	No
Anticonvulsants									
Davis et al. (2008)	Veterans (82)	Divalproex (mean: 2,309)	Monotherapy	8	CAPS	No	No	No	No
					CGI	No	NR	NR	NR
					DTS	No	NR	NR	NR
					TOP-8	No	NR	NR	NR
Tucker et al. (2007)	Civilians (38)	Topiramate (25 to 400)	Monotherapy	12	CAPS	No	Yes (.038)	No	No
					DTS	No	No	No	No
					TOP-8	Yes (.025)	No	No	No
					CGI	No	NR	NR	NR
Lindley et al. (2007)	Veterans (24)	Topiramate (50 to 200)	Augmentation	7	CAPS CGI PGI-I	No	Yes (<.05)	No	No
						No	NR	NR	NR
						No	NR	NR	NR
Davidson et al. (2007)	Civilians (232)	Tiagabine (2 to 16)	Monotherapy	12	CAPS	No	NR	NR	NR
					DTS	No	NR	NR	NR
					TOP-8	No	NR	NR	NR
					CGI	No	NR	NR	NR
Hertzberg et al. (1999)	Civilians and veterans (15)	Lamotrigine (50 to 500)	Monotherapy	12	DGRP	Yes	Yes	Yes	No
Adrenergic-inhibiting agents									
Neylan et al. (2006)	Veterans (63)	Guanfacin (1 to 3)	Augmentation	8	CAPS	No	No	No	No
					IES-R	No	No	No	No
					SQI	No	No	No	No
Raskind et al. (2007)	Veterans (40)	Prazosin (mean: 13)	Augmentation	8	CAPS	No	Yes, nightmares (.02)	NR	NR
					PSQI	NA	Yes (.008)	NR	NR
					CGI	Yes (.002)	NR	NR	NR
Taylor et al. (2008)	Civilians (13)	Prazosin (2 to 6)	Augmentation	7 (*crossover* at week 3)	PCL-C	Yes (<.05)	NR	NR	NR
					CGI	Yes (<.05)	NR	NR	NR
Raskind et al. (2003)	Veterans (10)	Prazosin (mean: 9.5)	Augmentation	20 (*crossover* at week 10)	CAPS	Yes (<.01)	Yes (<.001)	Yes (<.001)	Yes (<.001)
					CGI-C	Yes (<.01)	Yes	Yes	Yes
Benzodiazepines									
Braun et al. (1990)	Civilians and veterans (16)	Alprazolam (1.5 to 6)	Monotherapy	12 (crossover at week 5)	IES	No	No	No	NA

CAPS: Clinician-Administered PTSD Scale; CAPS-2: Clinician-Administered PTSD Scale, 1 week version; CGI: Clinical Global Impression; DGRP: Duke Global Rating for PTSD scale; DTS: Davidson Trauma Scale; IES-R: Impact Event Scale Revised; NA: not applicable; NR: not reported; PCL-M: Posttraumatic Stress Disorder Checklist Military version; PGI-I: Patient Global Impression-Improvement scale; PSQI: Pittsburgh Sleep Quality Index; SPRINT: Short PTSD Rating Interview; SQI: Subjective sleep quality; TOP-8: Treatment Outcomes PTSD Scale.

[a] When not reported, or no statistical significant difference was found, or was not reported by the authors. Cluster B: reexperiencing; cluster C: avoidance/numbing; Cluster D: hyperarousal.

8 weeks. At the end of the trial, 43% of participants showed a reduction of at least 30% in the global score of CAPS, with comparable improvements observed in each of the three symptom clusters.

Divalproex (mean: 1500 mg/day) was also employed in an eight-week trial (Goldberg et al., 2003) with civilian patients as a monotherapy (1 patient) and as an adjunctive treatment (6 patients) leading to a significant reduction in the symptoms of PTSD ($p<0.02$), particularly those of the avoidance and hyperarousal clusters, as measured by the *Posttraumatic Stress Disorder Symptoms Scale-Self Report* (PSS-SR) (Foa et al., 1993).

In a retrospective study, Davis et al. (2005) found that half of their fifty war veterans with PTSD treated with divalproate (three of them as monotherapy) achieved a final CGI score of ≤2 at the end of the therapeutic trial.

3.2.1.2. Lamotrigine

3.2.1.2.1. Randomized clinical trials. Hertzberg et al. (1999) administered lamotrigine as a monotherapy (mean: 380 mg/day) or placebo to 14 combat veterans and civilian patients for 12 weeks. Out of the 10 patients who were treated with lamotrigine, 5 (50%) were considered much or very much improved according to the *Physician Administered Duke Global Rating for PTSD Scale* (DGRP) (Davidson et al., 1998), as compared to 1 out of 4 (25%) who received placebo. Symptoms from the clusters B and C, in particular, showed marked reduction after treatment with lamotrigine. Given the small number of patients studied, however, these results must be taken with caution.

3.2.2. Level of evidence C

3.2.2.1. Carbamazepine

3.2.2.1.1. Open label studies. Looff et al. (1995) treated 28 children and teenagers victims of sexual abuse with carbamazepine (300–1200 mg/day). After 18 months, 22 patients (78.5%) were in full remission and the rest showed marked improvements, according to the subjective assessment of the research team.

Ten patients with PTSD were treated by Lipper et al. (1986) with carbamazepine for 5 weeks. At the end of the trial, 7 patients had CGI scores of 1 (markedly improved) or 2 (much improved). The symptoms of the reexperiencing cluster were the most improved.

Wolf et al. (1988) treated 10 combat veterans with carbamazepine and reported, based on the researchers' clinical judgement and the patients' self-report, a considerable improvement in impulsivity and in aggressiveness.

3.2.2.2. Topiramate

3.2.2.2.1. Randomized clinical trials. In a recent 12-week RCT, Tucker et al. (2007) assessed the efficacy of topiramate monotherapy (25–400 mg/day, mean: 150 mg/day) in 19 civilian patients with chronic PTSD who were compared to an equal number of patients receiving placebo. There were no significant differences between the groups in terms of the total scores of the CAPS, DTS and CGI. Topiramate-treated patients exhibited a significant decrease in reexperiencing symptoms (CAPS cluster B) and in TOP-8 scores at endpoint. Remission (defined here as CAPS total score <20) was achieved in twice as many patients in the topiramate-treated group ($n=8$, 42%) as compared to the placebo group ($n=4$, 21%).

In a 7-week, double-blind, randomized comparison of the efficacy of adjunctive topiramate and placebo for the treatment of chronic PTSD in veterans (Lindley et al., 2007), no differences were found between the groups. Besides, the topiramate-treated patients had a high drop-out rate (55%), mainly due adverse effects.

3.2.2.2.2. Open label studies. Berlant and Van Kammen (2002) described a naturalistic data review of medical records of 35 civilian patients with chronic PTSD who were treated with topiramate (12.5–500 mg/day), either as a monotherapy (7 patients) or as an adjunctive treatment (28 patients). After four weeks, not only a significant reduction in the scores of the *Posttraumatic Checklist-Civilian Version* (PCL-C) (Weathers et al., 1993) ($p<0.001$) was found but also 86% reported a decrease in the nightmares and in the intrusive thoughts.

In a 4-week trial, Berlant (2004) treated 33 civilian patients with chronic PTSD using topiramate (mean: 50 mg/day) as a monotherapy ($n=5$) or as an adjunctive therapy ($n=28$). Seventy-seven percent of those who completed the study ($n=30$) were considered responders (reduction of ≥30% in PCL-C scores). At the end of week 4, a significant decline was found in the PCL-C global scores (49%) ($p<0.001$) and in those of the reexperiencing (53%), avoidance/numbing (43%) and hyperarousal (48%) clusters.

3.2.2.3. Tiagabine

3.2.2.3.1. Randomized clinical trials. In a recent multisite, double-blind, placebo-controlled clinical trial, Davidson et al. (2007) assessed the efficacy and tolerability of tiagabine monotherapy (2–16 mg/day; mean: 11.2 mg/day) in the treatment of PTSD. Patients with a history of unresponsiveness to two or more pharmacological trials for PTSD were excluded from the study. Of the 232 participants randomized at baseline, only 141 completed the 12 weeks of treatment. Although tiagabine was well tolerated, it was not significantly superior to placebo, as assessed by the CAPS, DTS, CGI and TOP-8 final scores.

3.2.2.3.2. Open label studies. Connor et al. (2006) assessed the efficacy of tiagabine (mean: 12.5 mg/day) in 26 civilian patients in a two-stage study. In the first phase, an open trial with tiagabine led to a significant decrease in the scores of the SPRINT ($p<0.001$) between baseline and week 12. Next, the 18 patients who had improved during phase 1 were randomized 1:1 to twelve weeks of double-blind treatment, either continuing the tiagabine or switching to placebo. Somewhat surprisingly, both groups fared equally well and maintained the improvement achieved during the first phase.

3.2.2.4. Levetiracetam

3.2.2.4.1. Open label studies. In a retrospective naturalistic study with 35 civilian patients with chronic refractory PTSD, Kinrys et al. (2006) showed that adding levitiracetam (1000–3000 mg/day, mean: 1967 mg/day), a novel anticonvulsant, to antidepressants for 4–20 weeks led to a significant decrease in the scores of the PCL-C.

3.2.2.5. Phenytoin

3.2.2.5.1. Open label studies. Phenytoin was administered as a monotherapy to 9 combat veterans and civilian patients with PTSD. Blood levels were maintained within the range of 10 to 20 ng/ml for 3 months. At the end of this period, significant reductions in mean total scores of CAPS ($p=0.005$) were noted, as well as in each of its subscores ($p<0.05$). Treatment with phenytoin also resulted in social and functional improvement (Bremner et al., 2004).

3.2.3. Level of evidence D

3.2.3.1. Gabapentin

3.2.3.1.1. Anecdotal reports and case series. Hamner et al. (2001) published a retrospective series of 30 cases where gabapentin (300–3600 mg/day; mean: 1190 mg/day) was found to be effective as an adjunctive therapy for the treatment of certain PTSD symptoms, such as insomnia and nightmares.

3.2.3.2. Vigabatrin

3.2.3.2.1. Anecdotal reports and case series. Macleod (1996) reported 5 cases of PTSD in which vigabatrin (250–500 mg/day) led to a reduction of the exaggerated startle response and to an improvement of the sleep pattern.

3.3. Adrenergic-inhibiting agents

The increase of the noradrenergic function seen in dangerous situations can lead to the overconsolidation of memories in the amygdala

(Deebie and LeDoux, 2006; Shin et al., 2006). Alpha-1 adrenergic receptor stimulation in CNS disrupts sleep physiology, increases nightmares, enhances the secretion of corticotropin release factor (CRF)—which has anxiogenic properties and disrupts deep sleep—and favors the emergence of primitive alarm-related cognitive processing (Raskind et al., 2007). For all these reasons, centrally acting alpha-1 adrenergic receptor antagonists are a promising alternative for the treatment of nightmares, insomnia and other sleep-related PTSD symptoms.

3.3.1. Level of evidence B

3.3.1.1. Prazosin

3.3.1.1.1. Randomized clinical trials. In an 8-week, placebo-controlled trial, Raskind et al. (2007) compared the efficacy of prazosin (mean: 13 mg/day) and placebo in the treatment of 40 combat veterans with chronic PTSD and intractable nightmares and other sleep disturbances. In twenty cases, prazosin or placebo were added to a pre-existing therapeutic scheme. At the end of the study, patients treated with prazosin showed a significantly greater improvement in the frequency and intensity of trauma-related nightmares (according to the recurrent distressing dreams item of the CAPS), sleep quality (as measured by the *Pittsburgh Sleep Quality Index*, PSQI) (Buysse et al., 1989) and overall PTSD symptoms severity (according to the CGI-I). Nevertheless, a comparison of the total CAPS scores failed to show significant differences between the two groups at endpoint. It is noteworthy that prazosin reduced military trauma-related nightmares compared to nightmares of any kind and shifted dream characteristics from those typical of trauma-related nightmares toward those of regular dreams.

Taylor et al. (2008) investigated the efficacy of prazosin (2–6 mg/day; mean: 3.1 mg/day) as an augmentation strategy in 11 civilian patients with PTSD and distressing dreams. In this 7-week, classic crossover design study, patients completed random-order three-week long trials of prazosin and of placebo separated by a 1-week washout period. The author found that treatment with prazosin was associated with a greater total sleep time ($p<0.01$), REM sleep time ($p<0.01$) and mean REM period duration (total REM time per night divided by the number of REM periods per night) ($p<0.05$). The outcome of the PTSD symptoms, measured by the PCL-C and CGI-I, was significantly superior ($p<0.05$) when prazosin was administered instead of placebo.

In a 20-week, double-blind, placebo-controlled crossover RCT, Raskind et al. (2003) employed the CAPS and the CGI to measure the therapeutic efficacy of prazosin (mean: 9.5 mg/day) as an augmentation strategy in 10 veterans with chronic refractory PTSD. The authors reported that treatment with prazosin not only decreased the severity of nightmares ($p<0.01$) but also led to reductions in general posttraumatic symptomatology.

3.3.1.1.2. Open label studies. In a study with a complex methodological design, Taylor et al. (2006) studied the role of prazosin as an adjunctive therapy in the treatment of 11 civilian patients with refractory PTSD (6 patients using SSRIs, 6 using non-SSRIs antidepressants, 3 using buspirone and 2 using benzodiazepine or zolpidem). This study was divided in three phases. The first was a one-month open-label trial, where prazosin was used once a day (at night; mean: 3.2 mg/day) and the patients were evaluated with the PCL-C and CGI-S. The doses of prazosin were gradually increased until a reduction of at least 1 point in the item 2 of the PCL-C (repeated, disturbing dreams of a stressful experience) was achieved by 11 patients. At the end of this phase, PCL-C mean score had declined from 67 to 54 ($p<0.01$), while CGI-S average score decreased from 4.1 to 3.2 ($p<0.01$). In the second phase, neuropsychological testing was carried out. In the third phase, ten patients were treated for two weeks with prazosin b.i.d. with the maximum nighttime doses achieved in phase 1. At this point, mean CGI-S scores had dropped from 3.2 to 1.5 ($p<0.01$).

Peskind et al. (2003) treated 8 elderly veterans and a Holocaust survivor with chronic PTSD and refractory nightmares with prazosin (2–4 mg/day) for 8 weeks. According to the CGI-I scores, eight patients were moderate to very much improved by the end of the study. Prazosin substantially reduced nightmares as assessed by the specific CAPS item ($p<0.001$).

In a chart review study, Raskind et al. (2002) evaluated the use of adjunctive prazosin in 59 combat veterans with refractory PTSD and frequent nightmares. Patients were divided into 3 groups comprised of those who: 1) did not fill their prazosin prescriptions but returned for follow-up (controls, $n=8$); 2) initiated treatment with prazosin but failed to complete 8 weeks of treatment ($n=15$); and 3) finished 8 weeks of treatment with prazosin ($n=36$). For the sake of analysis, groups 2 and 3 were lumped together as those receiving prazosin. Patients were assessed with the CGI-I and with the item of the CAPS covering repeated distressing dreams. Reduction in the nightmares was significantly greater in patients taking prazosin ($p<0.0001$). The mean score of CGI-I as applied to nightmares also revealed a significant improvement in this group.

3.3.1.1.3. Anecdotal reports and case series. Daly et al. (2005) treated 23 veterans with complaints of nightmares (not necessarily associated with PTSD) with prazosin (1–6 mg/day). In 13 cases, prazosin was used as an adjunctive therapy. After 3 months, nightmares had remitted completely in 20 patients and partially in two.

Taylor and Raskind (2002) used prazosin (1–4 mg/day) as an adjunctive therapy in 5 patients with refractory PTSD. After 6 weeks, all patients attained an at least moderate improvement, according the CGI-I scores for general symptoms and for nightmares. The global score of the CAPS also decreased by at least 20 points in all patients.

3.3.2. Level of evidence C

3.3.2.1. Propranolol

3.3.2.1.1. Open label studies. In a study with 12 veterans with chronic PTSD (Kolb et al., 1984), the administration of propranolol (120–160 mg/day) significantly improved intrusive thoughts, nightmares, insomnia, outbursts of anger, exaggerated startle reaction and hypervigilance.

In a clinical trial with 11 children with acute PTSD secondary to sexual and/or physical abuse (Famularo et al., 1988), the use of propranolol at maximum dose of 2.5 mg/kg/day decreased intrusive thoughts and hyperarousal symptoms.

3.3.3. Level of evidence D

3.3.3.1. Guanfacine

3.3.3.1.1. Randomized clinical trials. Veterans with chronic PTSD who were either medication-free or on a stable therapeutic scheme were randomly assigned to be treated with guanfacine (mean: 2.4 mg/day) ($n=29$) or with placebo ($n=34$) for 8 weeks (Neylan et al., 2006). Guanfacine showed no effect on PTSD symptoms, subjective sleep quality, or general mood disturbances as measured by the CAPS, the *Impact of Event Scale-Revised* (IES-R) (Weiss and Marmar, 1997), the *Hamilton Depression Rating Scale* (Hamilton, 1960), the *Symptom Checklist-90 Revised* (SCL-90R) (Derogatis, 1977), the *Sleep Quality Index* (Buysse et al., 1989) and the *Quality of Life Inventory* (Frisch et al., 1992), and was associated with a number of side effects.

3.3.3.2. Clonidine

3.3.3.2.1. Open label studies. Harmon and Riggs (1996) provided clonidine patches to 7 pre-school children (3 to 6 year-old) with PTSD secondary to abuse and/or neglect. According to the teachers' and the attending physicians' opinion, there was a moderate to marked decrease in aggressiveness in all children and impulsivity, temper outbursts, emotional lability, hyperarousal, hypervigilance, generalized anxiety, oppositional behavior, insomnia or nightmares improved in 71% of the sample.

3.4. Opioid antagonists

Studies demonstrating increased central opioid activity in individuals with PTSD (van der Kolk et al., 1989) provided a rationale for preliminary trials of opioid antagonists in the treatment of PTSD symptoms, mainly numbing and avoidance. So far, however, results have been inconclusive.

3.4.1. Level of evidence D

3.4.1.1. Nalmefene

3.4.1.1.1. Open label studies. Glover (1993) administered nalmefene, a non-FDA approved oral opioid antagonist, to 18 combat veterans with chronic PTSD. Eight patients reported improvement at higher doses and showed a marked decrease of emotional numbing and of other PTSD symptoms, such as exaggerated startle response, flashbacks, nightmares, intrusive thoughts and rage attacks.

3.4.1.2. Naltrexone

3.4.1.2.1. Open label studies. Lubin et al. (2002) treated 8 patients with chronic PTSD with naltrexone (100–200 mg/day) for two weeks with disappointing results. Only clinically insignificant improvements in intrusive and hyperarousal symptoms were observed in the seven patients who completed the trial. All patients reported early side effects that severely curtailed the efforts to achieve higher doses.

3.5. Benzodiazepines

Benzodiazepines enhance GABAergic transmission and exert a inhibitory effect on the amygdala, a brain structure that is known to be involved in the processing of fear (Davis and Myers, 2002). Given that PTSD shares many of its symptoms with the anxiety disorders and that benzodiazepines are efficacious in the treatment of the latter (Hoffman and Mathew, 2008), there is rationale for using this class of drugs in the prevention and treatment of PTSD.

3.5.1. Level of evidence D

3.5.1.1. Alprazolam

3.5.1.1.1. Randomized clinical trials. In a 12-week crossover study, Braun et al. (1990) treated 16 patients suffering from chronic PTSD with alprazolam (1.5–6 mg/day) or placebo for 5 weeks, with a 2-week washout period in between. Although anxiety symptoms were significantly alleviated by treatment with alprazolam, no difference involving the PTSD symptoms *per se* were reported, as assessed by IES.

3.5.1.1.2. Open label studies. Gelpin et al. (1996) treated 13 victims of very recent accidents or terrorist attacks (range of 2–18 days after the traumatic event; mean: 6.7) with either clonazepam (mean: 2.7 mg/day) or alprazolam (2.5 mg/day) and compared them with 13 matched trauma survivors who were treated as usual (i.e. received no benzodiazepines). After 6 months, the benzodiazepine group did not differ from the controls in IES and *Mississippi Rating Scale for Combat-related PTSD-civilian trauma version* scores. Furthermore, 9 individuals from the benzodiazepine group and 3 controls were found to meet diagnostic criteria for PTSD according to the CAPS.

3.5.1.2. Temazepam

3.5.1.2.1. Open label studies. In a non-blinded trial, Mellman et al. (2002) randomized 21 victims of recent civilian trauma (mean: 14 days) who were manifesting PTSD symptoms to a 7-day course of temazepam (30 mg/day for 5 days followed by 15 mg/day for 2 day) or placebo. After six weeks, 55% of the subjects who were treated with temazepam and 27% of those who received placebo met diagnostic criteria for PTSD, according to the CAPS. Although treatment with temazepam led to sleep improvement, this positive effect did not persist after drug discontinuation.

3.6. Others

3.6.1. Level of evidence D

3.6.1.1. Cyproheptadine. Cyproheptadine is an antihistaminic medication that blocks $5HT_{2A}$ auto-receptors. Given that H_1 antagonism produces sedation and $5HT_{2A}$ blockade enhances serotonergic activity, antihistaminic drugs are considered a potentially useful pharmacological approach to the treatment of PTSD.

3.6.1.1.1. Open label studies. Clark et al. (1999a) medicated 16 patients with PTSD with cyproheptadine (4–8 mg/day) during a week. They used the Miami Veterans Administration Medical Center (VAMC) Post-Sleep Questionnaire to evaluate shifts in sleep patterns and the frequency of nightmares. However, cyproheptadine failed to show any consistent benefit and was poorly tolerated by patients.

3.6.1.2. Dehydroepiandrosterone (DHEA). It is well-known that cortisol can induce neuronal damage, particularly hyppocampal atrophy (Sapolsky, 2000). Dehydroepiandrosterone is an endogenous anti-glucocorticoid that protects neurons from the neurotoxic effects of cortisol (Kalimi et al., 1994; Kaminska et al., 2000). A recent study have reported a negative correlation between DHEA plasmatic levels and PTSD symptoms, i.e., the higher the DHEA levels, the lower the severity of the symptoms in individuals with PTSD (Rasmusson et al., 2004).

3.6.1.2.1. Open label studies. Sangeman et al. (Sageman and Brown, 2006) reported having used DHEA-S (dehydroepiandrosterone sulfate, 25–100 mg/day) to treat 5 women with severe chronic PTSD resulting from early life physical/sexual abuse. The participants were highly symptomatic despite having undergone extensive psychotherapy and years of pharmacotherapy. This trial led to decreases in dissociation, avoidance, numbing, reexperiencing, hyperarousal, anger, affective instability, and insomnia symptoms and an improvement in libido. Although preliminary in nature, these results are encouraging, particularly considering the severity and chronicity of PTSD in these patients.

3.6.1.3. Lithium carbonate. Several studies reported the efficacy of lithium in reducing aggression and impulsivity (Craft et al., 1987; Lewis, 2000; Tyrer et al., 1984; Forster et al., 1995). As these symptoms are frequently found in PTSD, it has been proposed that lithium might be useful in the treatment of this condition.

3.6.1.3.1. Open label studies. Kitchner and Greenstein (1985) used lithium (300–600 mg/day) to treat 5 veterans with refractory PTSD. Four patients reported improvements in anxiety, irritability, rage and insomnia. The fifth patient improved only when propranolol (10 mg/day) was added to augment lithium.

4. Discussion

Antidepressants are considered the primary class of medications for the treatment of PTSD. Given that several RCTs have repeatedly demonstrated their efficacy (Brady et al., 2000; Connor et al., 1999; Davidson et al., 2001; Marshall et al., 2001a; Neylan et al., 2001; Tucker et al., 2001; van der Kolk et al., 1994), it is now well established that SSRIs are the first-line pharmacotherapy for PTSD (Ursano et al., 2004). Further options include the dual action selective serotonin and noradrenaline reuptake inhibitors, tricyclics, monoaminoxidase inhibitors and others (nefazodone, bupropion etc.). The limited number of RCTs assessing alternative medications to be employed when patients do not tolerate or not respond to antidepressants poses a challenge to the clinicians. The authors of the present review decided not to limit the present systematic review to RCTs since open trials and case series are often the first evidence supporting innovative treatment (Albrecht et al., 2005). Indeed, clinicians in their daily practice frequently have

no controlled clinical trial-based evidence to guide them through the decision-making process and have to rely on the best available piece of evidence. Given that the majority of the studies reviewed here suffered from methodological shortcomings, there is currently no medication for the treatment of PTSD within the level A of evidence other than antidepressants. Level B of evidence was achieved by risperidone, olanzapine, lamotrigine, valproate and prazosin. Seven medications warranted level C and 13 level D (Table 1).

In four out of six RCTs with risperidone, this medication was shown to be superior to placebo in reducting overall PTSD severity (Bartzokis et al., 2005; Monnelly et al., 2003; Padala et al., 2006; Reich et al., 2004). Only Hamner et al. (2003b) and Rothbaum et al. (2008) failed to find significant differences. It must be noted, however, that the sample investigated by Hamner and his collaborators was composed exclusively by war veterans, a population that is characterized by high levels of refractoriness (Mohamed and Rosenheck, 2008) and that their study duration (5 weeks) was the shortest of all the five RCTs while Rothbaum and colleagues' study was conducted with a small number of patients refractory to first-line treatment with sertraline. It is also worth mentioning that none of these six RCTs have demonstrated the efficacy of risperidone on the symptoms of the avoidance/numbing cluster.

As noted above, the two existing RCTs on olanzapine in PTSD produce conflicting results: while Stein et al. (2002) found that olanzapine was superior to placebo as an augmentation therapy in the treatment of 19 male war veterans with refractory PTSD, Butterfield et al. (2001) found no advantage for olanzapine in a sample of 15 civilian PTSD patients (14 women, with 4 drop-outs during the study). The inconsistency of the results could be ascribed to several factors including differences in treatment strategies (augmentation *vs.* monotherapy), demographic make-up of the sample, type of trauma, level of treatment resistance, and time elapsed since the traumatic event.

It must be kept in mind that the efficacy of the antipsychotics in the treatment of refractory PTSD may not reflect any specific action on posttraumatic symptoms, but rather their effects on non-specific symptoms, such as insomnia, nightmares, and associated psychotic ideation. It is also important to note that since these trials were essentially short-term ones, the possibility of the occurrence of severe side effects such as metabolic syndrome and tardive dyskinesia should remain a major concern.

Although anticonvulsants have assumed an ever increasing role in the psychiatric armamentarium, being now used regularly to treat mood (Carvalho et al., 2007) and anxiety disorders (Mula et al., 2007), their real worth in the treatment of post-traumatic stress remains uncertain. Studies on the efficacy of anticonvulsants in PTSD far outnumber those of antipsychotics, but the former are clearly methodologically inferior to the latter. Only six RCTs were conducted with anticonvulsants. Most studies described a decrease in the severity PTSD symptoms after anticonvulsants were added to a pre-existing therapeutic scheme as an augmentation strategy. Hertzberg et al. (1999) reported that lamotrigine as a monotherapy was effective in reducing general symptoms, reexperiencing and avoidance/numbing, but not hyperarousal, in treatment-refractory PTSD. Steiner et al. (2007) demonstrated that divalproex sodium, especially at doses between 500 and 1500 mg/day, could ameliorate PTSD symptoms. It should be noted that this study did not compare the use of divalproate against that of placebo. However, in a placebo-controlled, double-blind study, Davis et al. (2008) found that divalproex had no discernible effects on the chronic PTSD symptoms of veterans, even in high doses. Tucker et al. (2007) reported the effectiveness of topiramate as a monotherapy in ameliorating symptoms of reexperiencing (but not the global scores of PTSD). These findings were replicated by Lindley et al. (2007), who used topiramate as an augmentation strategy. Davidson et al. (2007) failed to demonstrate the superiority of tiagabine over placebo in the treatment of 232 civilian patients with PTSD, as determined by four difference outcomes measures, even after excluding patients with history of unresponsiveness to PTSD treatment.

Prazosin, an adrenergic-inhibiting agent, is a promising alternative in the treatment of PTSD, particularly when trauma-related nightmares and sleep disturbances are prominent symptoms, as shown by three recent RCTs. Taylor et al. (2008) found that prazosin not only improved the physiological patterns of sleep and produced positive qualitative changes in the character of pathological dreams, but also reduced overall PTSD severity, as measured by PCL-C. Raskind et al. (2007) showed a significant reduction in nightmares (through the distressing dreams item of the CAPS), improvement of sleep quality (as measured by the PSQI) and decrease of the severity of PTSD symptoms (assessed through the CGI-I) in veterans medicated with prazosin, as compared to those treated with placebo. Nevertheless, no significant differences were found in CAPS total scores. Finally, Raskind et al. (2003) reported that prazosin was effective for treating symptoms of the re-experiencing, avoidance/numbing, and hyperarousal clusters in treatment-resistant PTSD. Other adrenergic-inhibiting agents such as propranolol and clonidine were not yet evaluated by RCTs, but the few open-label studies published so far suggest that these drugs can alleviate some sleep disturbances (i.e. nightmares) and especially hyperarousal symptoms. A recent RCT showed that guanfacine (either as an augmentation strategy or as monotherapy) was ineffective in the treatment of PTSD symptoms (Neylan et al., 2006).

Benzodiazepines are frequently prescribed by physicians in the aftermath of a traumatic event in an effort to prevent the development of psychological sequelae or, if PTSD eventually arises, to reduce active post-traumatic symptoms, like hypervigilance, or control associated non-specific behavioral disturbances, such as marked anxiety or agitation.

Thus far, there is no compelling scientific evidence of the effectiveness of benzodiazepines either in the prevention of PTSD or in the treatment of its core symptoms although clinical experience suggests that they may improve sleep and agitation, at least in the short term. These limited advantages must be weighted against the marked potential for addiction that characterizes this class of drugs, particularly considering that PTSD patients have higher rates of drug abuse/dependence than the general population (Kessler et al., 1995). Recently, Westra et al. (2004) have reported that individuals with anxiety disorders who take benzodiazepines exhibit a reduced capacity to remember material presented in cognitive-behavioral therapy and hypothesized that this memory impairment may account for the lower efficacy of this modality of psychotherapy in these patients (Westra et al., 2004). In addition, a few studies suggest that benzodiazepines may contribute to the development and/or chronification of posttraumatic symptoms (Gelpin et al., 1996; Mellman et al., 2002). Following the fundamental principle of Medicine, "primum non nocere", future RCTs should further investigate the potentially iatrogenic effects of benzodiazepines before they can be safely recommended for the treatment of PTSD.

The scientific evidence supporting the use of opioids antagonists in PTSD is still limited: two existing open-label trials showed disappointing results (Glover, 1993; Lubin et al., 2002).

Although the use of cyproheptadine in the treatment of PTSD has a good rationale, the only open-label trial available found low efficacy and a high rate of adverse effects. Others drugs, such as dehydroepiandrosterone and propranolol, may eventually turn out to be clinically useful, but for now the few existing studies suffer from methodological limitations.

The studies reviewed here must be taken with caution for several reasons. First, many of these studies failed to specify whether the medications were employed as a monotherapy or as an augmentation strategy. This is a serious methodological problem that not only jeopardizes the comparability of the studies, but also limits their clinical usefulness. Second, the majority of the case reports and open label trials reported positive results with several medications that had not yet been otherwise rigorously evaluated in the this context. A publication bias could explain the predominance of favorable results

in this literature, given that editors and authors tend to favor positive findings. Third, the majority of these studies were carried out with combat veterans, a population that is notoriously refractory to conventional treatment, making the results difficult to extrapolate to civilian samples. Fourth, the criteria for therapeutic response currently adopted are based on partial improvement rather than on full remission and may overestimate the clinical significance of even modest symptomatic improvement in PTSD. For instance, when the definition of clinical response adopted is a reduction ≥30% in CAPS scores, it is likely that many patients considered to be responders are continuing to suffer from clinically relevant subsyndromal PTSD, a condition that is known to be associated with substantial impairment (Marshall et al., 2001b). Finally, the system of classification of the level of scientific evidence used in this review did not take into consideration the number of participants in the studies.

5. Conclusions

The well-known difficulties in managing PTSD are aggravated when the patient does not respond to or do not tolerate treatment with antidepressants. Our review of the literature suggested that, in these cases, there are a few alternatives to be considered. Risperidone is the medication with the strongest empirical support for a role as an alternative treatment of PTSD, particularly as an augmentation strategy, despite not having its efficacy demonstrated on avoidance and emotional numbing symptoms. Given its safety profile, risperidone can be envisaged as an effective add-on therapy in cases where patients could not reap full benefits from the treatment with SSRIs.

Another promising medication is prazosin, particularly in cases where trauma-related nightmares and insomnia are prominent complaints. This finding highlights the facts that symptoms of PTSD are heterogeneous and each of them may respond differently to specific medication and provides a strong stimulus for investigating new symptom-specific drugs. Unfortunately, the symptom cluster that is associated with more severe functional impairment—avoidance/numbing—is the one that is less responsive to available alternative pharmacotherapic agents.

On a negative note, it was surprising to find that one of the most deeply entrenched habits of clinicians, that of treating acutely traumatized patients with benzodiazepines in an attempt to minimize putative psychological sequelae, not only lacks empirical support but may also have the opposite effect. Efforts should be made to educate clinicians about the proper management of acute psychological trauma.

It must be emphasized that the choice of a medication should take into consideration not only the nature and the severity of the posttraumatic symptoms, but also the existence of associated comorbidities, the history of previous treatment trials, the possibility of drug interactions, the occurrence of side effects, and the physical and psychological conditions of the patient. Hopefully, future controlled randomized trials with newer drugs will be able to address many of the uncertainties that plague current knowledge about the treatment of PTSD and teach us innovative ways to reduce the suffering and the disability associated with this disorder.

Conflict of interest

Drs. Berger, Mendlowicz, Marques-Portella, Figueira, Fontenelle and Marmar have no conflicts of interest. Dr. Kinrys has received research grants and support from AstraZeneca, Bristol-Myers Squibb, CNS Response, Cephalon, Elan, Eli Lilly, Forest, GlaxoSmithKline, Janssen, Pfizer, Sanofi-Aventis, Sepracor, Takeda, and UCB Pharma.

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References

Ahearn EP, Mussey M, Johnson C, Krohn A, Krahn D. Quetiapine as an adjunctive treatment for post-traumatic stress disorder: an 8-week open-label study. Int Clin Psychopharmacol 2006;21:29–33.
Albrecht J, Meves A, Bigby M. Case reports and case series from Lancet had significant impact on medical literature. J Clin Epidemiol 2005;58:1227–32.
Albucher RC, Liberzon I. Psychopharmacological treatment in PTSD: a critical review. J Psychiatr Res 2002;36:355–67.
American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Press; 1994.
Asnis GM, Kohn SR, Henderson M, Brown NL. SSRIs versus non-SSRIs in post-traumatic stress disorder—an update with recommendations. Drugs 2004;64:383–404.
Ballenger JC. Remission rates in patients with anxiety disorders treated with paroxetine. J Clin Psychiatry 2004;65:1696–707.
Bartzokis G, Lu PH, Turner J, Mintz J, Saunders CS. Adjunctive risperidone in the treatment of chronic combat-related posttraumatic stress disorder. Biol Psychiatry 2005;57:474–9.
Berlant J. Prospective open-label study of add-on and monotherapy topiramate in civilians with chronic nonhallucinatory posttraumatic stress disorder. BMC Psychiatry 2004;4:24.
Berlant J, Van Kammen DP. Open-label topiramate as primary or adjunctive therapy in chronic civilian posttraumatic stress disorder: a preliminary report. J Clin Psychiatry 2002;63:15–20.
Blake DD, Weathers FW, Nagy lM. A clinical rating scale for assessing current and lifetime PTSD: the CAPS 1. Behav Ther 1990;18:187–8.
Brady K, Pearlstein T, Asnis GM, Baker D, Rothbaum B, Sikes CR, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder—a randomized controlled trial. JAMA 2000;283:1837–44.
Braun P, Greenberg D, Dasberg H, Lerer B. Core symptoms of posttraumatic stress disorder unimproved by alprazolam treatment. J Clin Psychiatry 1990;51:236–8.
Bremner JD, Mletzko T, Welter S, Siddiq S, Reed L, Williams C, et al. Treatment of posttraumatic stress disorder with phenytoin: an open-label pilot study. J Clin Psychiatry 2004;65:1559–64.
Briere J. Trauma symptoms checklist for children. Psychological Assessment Resources, Inc; 1996.
Butler RW, Mueser KT, Sprock J, Braff DL. Positive symptoms of psychosis in posttraumatic stress disorder. Biol Psychiatry 1996;39:839–44.
Butterfield MI, Becker ME, Connor KM, Sutherland S, Churchill LE, Davidson JRT. Olanzapine in the treatment of post-traumatic stress disorder: a pilot study. Int Clin Psychopharmacol 2001;16:197–203.
Buysse DJ, Reynolds CFI, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213.
Carvalho AF, Cavalcante JL, Castelo MS, Lima MCO. Augmentation strategies for treatment-resistant depression: a literature review. J Clin Pharm Ther 2007;32: 415–28.
Clark RD, Canive JM, Calais LA, Qualls C, Brugger RD, Vosburgh TB. Cyproheptadine treatment of nightmares associated with posttraumatic stress disorder. J Clin Psychopharmacol 1999a;19:486–7.
Clark RD, Canive JM, Calais LA, Qualls CR, Tuason VB. Divalproex in posttraumatic stress disorder: an open-label clinical trial. J Trauma Stress 1999b;12:395–401.
Connor KM, Davidson JRT. Further psychometric assessment of the TOP-8: a brief interview-based measure of PTSD. Depress Anxiety 1999;9:135–7.
Connor KM, Davidson JRT. SPRINT: a brief global assessment of post-traumatic stress disorder. Int Clin Psychopharmacol 2001;16:279–84.
Connor KM, Sutherland SM, Tupler LA, Malik ML, Davidson JR. Fluoxetine in post-traumatic stress disorder. Randomised, double-blind study. Br J Psychiatry 1999;175:17–22.
Connor KM, Davidson JRT, Weisler RH, Zhang W, Abraham K. Tiagabine for posttraumatic stress disorder: effects of open-label and double-blind discontinuation treatment. Psychopharmacology 2006;184:21–5.
Craft M, Ismail IA, Krishnamurti D, Mathews J, Regan A, Seth RV, et al. Lithium in the treatment of aggression in mentally handicapped patients. A double-blind trial. Br J Psychiatry 1987;150:685–9.
Cullen N, Goddard GV. Kindling in hypothalamus and transfer to the ipsilateral amygdala. Behav Biol 1975;15:119–31.
Daly CM, Doyle ME, Radkind M, Raskind E, Daniels C. Clinical case series: the use of prazosin for combat-related recurrent nightmares among Operation Iraqi Freedom combat veterans. Mil Med 2005;170:513–5.
David D, De Faria L, Lapeyra O, Mellman TA. Adjunctive risperidone treatment in combat veterans with chronic PTSD. J Clin Psychopharmacol 2004;24:556–9.
David D, De Faria L, Mellman TA. Adjunctive risperidone treatment and sleep symptoms in combat veterans with chronic PTSD. Depress Anxiety 2006;23:489–91.
Davidson JRT, Book SW, Colket JT, Tupler LA, Roth S, David D, et al. Assessment of a new self-rating scale for post-traumatic stress disorder. Psychol Med 1997;27:153–60.
Davidson JRT, Smith RD, Malik M, Tupler LA. Fluvoxamine in civilians with PTSD. J Clin Psychopharmacol 1998;18:93–5.
Davidson J, Pearlstein T, Londborg P, Brady KT, Rothbaum B, Bell J, Maddock R, et al. Efficacy of sertraline in preventing relapse of posttraumatic stress disorder: results of a 28-week double-blind, placebo-controlled study. Am J Psychiatry 2001;158: 1974–81.
Davidson J, Baldwin D, Stein DJ, Kuper E, Benattia I, Ahmed S, et al. Treatment of posttraumatic stress disorder with venlafaxine extended release: a 6-month randomized controlled trial. Arch Gen Psychiatry 2006;63:1158–65.

Davidson JRT, Brady KM, Mellman TAM, Stein MBM, Pollack MHM. The efficacy and tolerability of tiagabine in adult patients with post-traumatic stress disorder. J Clin Psychopharmacol 2007;27:85–8.
Davis M, Myers KM. The role of glutamate and gamma-aminobutyric acid in fear extinction: clinical implications for exposure therapy. Biol Psychiatry 2002;52: 998–1007.
Davis LL, Ambrose SM, Newell JM, Waldrop E, Cates M, Ward LC. Divalproex for the treatment of posttraumatic stress disorder: a retrospective chart review. Int J Psychiatr Clin Pract 2005;9:278–83.
Davis LL, Davidson JRT, Ward LC, Bartolucci A, Bowden CL, Petty F. Divalproex in the treatment of posttraumatic stress disorder: a randomized, double-blind, placebo-controlled trial in a veteran population. J Clin Psychopharmacol 2008;28:84–8.
Deebie JACE, LeDoux JE. Noradrenergic signaling in the amygdala contributes to the reconsolidation of fear memory. treatment implications for PTSD. Ann N Y Acad Sci 2006;1071:521–4.
Derogatis LR. The SCL-90R: scoring, administration and procedures manual: II. Baltimore: Johns Hopkins University School of Medicine, Clinical Psychometrics Unit; 1977.
Eidelman I, Seedat S, Stein DJ. Risperidone in the treatment of acute stress disorder in physically traumatized in-patients. Depress Anxiety 2000;11:187–8.
Famularo R, Kinscherff R, Fenton T. Propranolol treatment for childhood posttraumatic stress disorder, acute type. A pilot study. Am J Dis Child 1988;142:1244–7.
Fesler FA. Valproate in combat-related posttraumatic-stress-disorder. J Clin Psychiatry 1991;52:361–4.
Filteau MJ, Leblanc J, Bouchard RH. Quetiapine reduces flashbacks in chronic posttraumatic stress disorder. Can J Psychiatry 2003;48:282–3.
Foa EB, Riggs DS, Dancu CV, Rothbaum BO. Reliability and validity of a brief instrument for assessing posttraumatic stress disorder. J Trauma Stress 1993;6:459–73.
Forster PL, Schoenfeld FB, Marmar CR, Lang AJ. Lithium for irritability in posttraumatic-stress-disorder. J Trauma Stress 1995;8:143–9.
Frisch MB, Cornell J, Villanueva M, Retzlaff PJ. Clinical validation of the Quality of Life Inventory: a measure of life satisfaction for use in treatment planning and outcome assessment. Psychol Assess 1992;4:92–101.
Gelpin E, Bonne O, Peri T, Brandes D, Shalev AY. Treatment of recent trauma survivors with benzodiazepines: a prospective study. J Clin Psychiatry 1996;57:390–4.
Glover H. A preliminary trial of nalmefene for the treatment of emotional numbing in combat veterans with post-traumatic stress disorder. Isr J Psychiatry Relat Sci 1993;30:255–63.
Goldberg JF, Cloitre M, Whiteside JE, Han H. An open-label pilot study of divalproex sodium for posttraumatic stress disorder related to childhood abuse. Curr Ther Res Clin Exp 2003;64:45–54.
Guy W. ECDEU assessment manual for psychopharmacology. Washinton DC: National Institute of Mental Health; 1976.
Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;12: 56–62.
Hamner MB, Brodrick PS, Labbate LA. Gabapentin in PTSD: a retrospective, clinical series of adjunctive therapy. Ann Clin Psychiatry 2001;13:141–6.
Hamner MB, Deitsch SE, Brodrick PS, Ulmer HG, Lorberbaum JP. Quetiapine treatment in patients with posttraumatic stress disorder: an open trial of adjunctive therapy. J Clin Psychopharmacol 2003a;23:15–20.
Hamner MB, Faldowski RA, Ulmer HG, Frueh BC, Huber MG, Arana GW. Adjunctive risperidone treatment in post-traumatic stress disorder: a preliminary controlled trial of effects on comorbid psychotic symptoms. Int Clin Psychopharmacol 2003b;18:1–8.
Hamner MB, Robert S, Frueh BC. Treatment-resistant posttraumatic stress disorder: strategies for intervention. CNS Spectr 2004;9:740–52.
Harmon RJ, Riggs PD. Clonidine for posttraumatic stress disorder in preschool children. J Am Acad Child Adolesc Psych 1996;35:1247–9.
Hertzberg MA, Butterfield MI, Feldman ME, Beckham JC, Sutherland SM, Connor KM, et al. A preliminary study of lamotrigine for the treatment of posttraumatic stress disorder. Biol Psychiatry 1999;45:1226–9.
Hoffman EJ, Mathew SJ. Anxiety disorders: a comprehensive review of pharmacotherapies. Mt Sinai J Med 2008;75:258–62.
Iancu I, Rosen Y, Moshe K. Antiepileptic drugs in posttraumatic stress disorder. Clin Neuropharmacol 2002;25:225–9.
Jakovljevic M, Sagud M, Mihaljevic-Peles A. Olanzapine in the treatment-resistant, combat-related PTSD—a series of case reports. Acta Psychiatr Scand 2003;107: 394–6.
Jefferson JW. Lamotrigine in psychiatry: pharmacology and therapeutics. CNS Spectr 2005;10:224–32.
Kalimi M, Shafagoj Y, Loria R, Padgett D, Regelson W. Anti-glucocorticoid effects of dehydroepiandrosterone (DHEA). Mol Cell Biochem 1994;131:99–104.
Kaminska M, Harris J, Gijsbers K, Dubrovsky B. Dehydroepiandrosterone sulfate (DHEAS) counteracts decremental effects of corticosterone on dentate gyrus LTP. implications for depression. Brain Res Bull 2000;52:229–34.
Kay SR, Fiszbein A, Opler LA. The positive and negative syndrome scale (PANSS) for schizophrenia. Schizophr Bull 1987;13:261–76.
Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Posttraumatic stress disorder in the National Comorbidity Survey. Arch Gen Psychiatry 1995;52:1048–60.
Kinrys G, Wygant LE, Pardo TB, Melo M. Levetiracetam for treatment-refractory posttraumatic stress disorder. J Clin Psychiatry 2006;67:211–4.
Kitchner I, Greenstein R. Low-dose lithium-carbonate in the treatment of post traumatic stress disorder. Mil Med 1985;150:378–81.
Kolb LC, Burris B, Griffiths S. Propranolol and clonidine in the treatment of chronic posttraumatic stress of war. In: Van Der Kolk BA, editor. Posttraumatic stress disorder: psychological and biological sequelae. Washington DC: American Psychiatric Press; 1984. p. 97–107.
Kozaric-Kovacic D, Pivac N, Muck-Seler D, Rothbaum BO. Risperidone in psychotic combat-related posttraumatic stress disorder: an open trial. J Clin Psychiatry 2005;66:922–7.
Lambert MT. Aripiprazole in the management of post-traumatic stress disorder symptoms in returning Global War on Terrorism veterans. Int Clin Psychopharmacol 2006;21:185–7.
Leon AC, Shear MK, Portera L, Kleman GL. Assessing impairment in patients with panic disorder: the Sheehan Disability Scale. Soc Psychiatry Psychiatr Epidemiol 1992;27:78–82.
Lewis CF. Successfully treating aggression in mentally ill prison inmates. Psychiatr Q 2000;71:331–43.
Lindley SE, Carlson EB, Hill K. A randomized, double-blind, placebo-controlled trial of augmentation topiramate for chronic combat-related posttraumatic stress disorder. J Clin Psychopharmacol 2007;27:677–81.
Lipper S, Davidson JR, Grady TA, Edinger JD, Hammett EB, Mahorney SL, et al. Preliminary study of carbamazepine in post-traumatic stress disorder. Psychosomatics 1986;27:849–54.
Looff D, Grimley P, Kuller F, Martin A, Shonfield L. Carbamazepine for Ptsd. J Am Acad Child Adolesc Psych 1995;34:703–4.
Lubin G, Weizman A, Shmushkevitz M, Valevski A. Short-term treatment of post-traumatic stress disorder with naltrexone: an open-label preliminary study. Hum Psychopharmacol 2002;17:181–5.
Macleod AD. Vigabatrin and posttraumatic stress disorder. J Clin Psychopharmacol 1996;16:190–1.
Marshall RD, Beebe KL, Oldham M, Zaninelli R. Efficacy and safety of paroxetine treatment for chronic PTSD: a fixed-dose, placebo-controlled study. Am J Psychiatry 2001a;158:1982–8.
Marshall RD, Olfson M, Hellman F, Blanco C, Guardino M, Struening EL. Comorbidity, impairment, and suicidality in subthreshold PTSD. Am J Psychiatry 2001b;158: 1467–73.
Mellman TA, Bustamante V, David D, Fins AI. Hypnotic medication in the aftermath of trauma. J Clin Psychiatry 2002;63:1183–4.
Mohamed S, Rosenheck RA. Pharmacotherapy of PTSD in the U.S. Department of Veterans Affairs: diagnostic- and symptom-guided drug selection. J Clin Psychiatry 2008;69:959–65.
Monnelly EP, Ciraulo DA, Knapp C, Keane T. Low-dose risperidone as adjunctive therapy for irritable aggression in posttraumatic stress disorder. J Clin Psychopharmacol 2003;23:193–6.
Mula MM, Pini SM, Cassano GBM. The role of anticonvulsant drugs in anxiety disorders: a critical review of the evidence. J Clin Psychopharmacol 2007;27:263–72.
Neylan TC, Metzler TJ, Schoenfeld FB, Weiss DS, Lenoci M, Best SR, et al. Fluvoxamine and sleep disturbances in posttraumatic stress disorder. J Trauma Stress 2001;14: 461–7.
Neylan TC, Lenoci M, Samuelson KW, Metzler TJ, Henn-Haase C, Hierholzer RW, et al. No improvement of posttraumatic stress disorder symptoms with guanfacine treatment. Am J Psychiatry 2006;163:2186–8.
Nutt DJ. The psychobiology of posttraumatic stress disorder. J Clin Psychiatry 2000;61: 24–9.
Otte C, Wiedemann K, Yassouridis A, Kellner M. Valproate monotherapy in the treatment of civilian patients with non-combat-related posttraumatic stress disorder: an open-label study. J Clin Psychopharmacol 2004;24:106–8.
Overall JE, Gorham DR. Brief Psychiatric Rating Scale (BPRS): recent developments in ascertainment and scaling. Psychopharmacol Bull 1988;24:97–9.
Padala PR, Madison J, Monnahan M, Marcil W, Price P, Ramaswamy S, et al. Risperidone monotherapy for post-traumatic stress disorder related to sexual assault and domestic abuse in women. Int Clin Psychopharmacol 2006;21:275–80.
Peskind ER, Bonner LT, Hoff DJ, Raskind MA. Prazosin reduces trauma-related nightmares in older men with chronic posttraumatic stress disorder. J Geriatr Psychiatry Neurol 2003;16:165–71.
Petty F, Brannan S, Casada J, Davis LL, Gajewski V, Kramer GL, et al. Olanzapine treatment for post-traumatic stress disorder: an open-label study. Int Clin Psychopharmacol 2001;16:331–7.
Petty F, Davis LL, Nugent AL, Kramer GL, Teten A, Schmitt A, et al. Valproate therapy for chronic, combat-induced posttraumatic stress disorder. J Clin Psychopharmacol 2002;22:100–1.
Pivac N, Kozaric-Kovacic D, Muck-Seler D. Olanzapine versus fluphenazine in an open trial in patients with psychotic combat-related post-traumatic stress disorder. Psychopharmacology 2004;175:451–6.
Raskind MA, Dobie DJ, Kanter ED, Petrie EC, Thompson CE, Peskind ER. The alpha1-adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. J Clin Psychiatry 2000;61: 129–33.
Raskind MA, Thompson C, Petrie EC, Dobie DJ, Rein RJ, Hoff DJ, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry 2002;63:565–8.
Raskind MA, Peskind ER, Kanter ED, Petrie EC, Radant A, Thompson CE, et al. Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psychiatry 2003;160:371–3.
Raskind MA, Peskind ER, Hoff DJ, Hart KL, Holmes HA, Warren D, et al. A parallel group placebo controlled study of prazosin for trauma nightmares and sleep disturbance in combat veterans with posttraumatic stress disorder. Biol Psychiatry 2007;61: 928–34.
Rasmusson AM, Vasek J, Lipschitz DS, Vojvoda D, Mustone ME, Shi Q, et al. An increased capacity for adrenal DHEA release is associated with decreased avoidance and negative mood symptoms in women with PTSD. Neuropsychopharmacology 2004;29:1546–57.
Reich DB, Winternitz S, Hennen J, Watts T, Stanculescu C. A preliminary study of risperidone in the treatment of posttraumatic stress disorder related to childhood abuse in women. J Clin Psychiatry 2004;65:1601–6.
Richelson E. Preclinical pharmacology of neuroleptics: focus on new generation compounds. J Clin Psychiatry 1996;57:4–11.

Robert S, Hamner MB, Kose S, Ulmer HG, Deitsch SE, Lorberbaum JP. Quetiapine improves sleep disturbances in combat veterans with PTSD—sleep data from a prospective, open-label study. J Clin Psychopharmacol 2005;25:387–8.
Rothbaum BO, Killeen TK, Davidson JRT, Brady KT, Connor KM, Heekin MH. Placebo-controlled trial of risperidone augmentation for selective serotonin reuptake inhibitor-resistant civilian posttraumatic stress disorder. J Clin Psychiatry 2008;69: 520–5.
Sageman S, Brown RP. 3-acetyl-7-oxo-dehydroepiandrosterone for healing treatment-resistant posttraumatic stress disorder in women: 5 case reports. J Clin Psychiatry 2006;67:493–6.
Sapolsky RM. Glucocorticoids and hippocampal atrophy in neuropsychiatric disorders. Arch Gen Psychiatry 2000;57:925–35.
Schaffer A, Zuker P, Levitt A. Randomized, double-blind pilot trial comparing lamotrigine versus citalopram for the treatment of bipolar depression. J Affect Disord 2006;96:95–9.
Schoenfeld FB, Marmar CR, Neylan HC. Current concepts in pharmacotherapy for posttraumatic stress disorder. Psychiatr Serv 2004;55:519–31.
Shin LM, Rauch SL, Pitman RK. Amygdala, medial prefrontal cortex, and hippocampal function in PTSD. Ann N Y Acad Sci 2006;1071:67–79.
States HS, St.Dennis CD. Chronic sleep disruption and the reexperiencing cluster of posttraumatic stress disorder symptoms are improved by olanzapine: brief review of the literature and a case-based series. Primary Care Companion J Clin Psychiatry 2003;5:74–9.
Stathis S, Martin G, McKenna JG. A preliminary case series on the use of quetiapine for posttraumatic stress disorder in juveniles within a youth detention center. J Clin Psychopharmacol 2005;25:539–44.
Stein MB, Kline NA, Matloff JL. Adjunctive olanzapine for SSRI-resistant combat-related PTSD: a double-blind, placebo-controlled study. Am J Psychiatry 2002;159:1777–9.
Stein DJ, Ipser JC, Seedat S. Pharmacotherapy for post traumatic stress disorder (PTSD). Cochrane Database Syst Rev 2006;1:CD 002795.
Steiner H, Saxena KS, Carrion V, Khanzode LA, Silverman M, Chang K. Divalproex sodium for the treatment of PTSD and conduct disordered youth: a pilot randomized controlled clinical trial. Child Psychiatry Hum Dev 2007;38:183–93.
Taylor F, Raskind MA. The alpha 1-adrenergic antagonist prazosin improves sleep and nightmares in civilian trauma posttraumatic stress disorder. J Clin Psychopharmacol 2002;22:82–5.
Taylor FB, Lowe K, Thompson C, Mcfall MM, Peskind ER, Kanter ED, et al. Daytime prazosin reduces psychological distress to trauma specific cues in civilian trauma posttraumatic stress disorder. Biol Psychiatry 2006;59:577–81.
Taylor FB, Martin P, Thompson C, Williams J, Mellman TA, Gross C, et al. Prazosin effects on objective sleep measures and clinical symptoms in civilian trauma posttraumatic stress disorder: a placebo-controlled study. Biol Psychiatry 2008;63:629–32.
Tucker P, Zaninelli R, Yehuda R, Ruggiero L, Dillingham K, Pitts CD. Paroxetine in the treatment of chronic posttraumatic stress disorder: results of a placebo-controlled, flexible-dosage trial. J Clin Psychiatry 2001;62:860–8.
Tucker P, Trautman RP, Wyatt DB, Thompson J, Wu SC, Capece JA, et al. Efficacy and safety of topiramate monotherapy in civilian posttraumatic stress disorder: a randomized, double-blind, placebo-controlled study. J Clin Psychiatry 2007;68: 201–6.
Tyrer S, Walsh A, Edwards DE, Berney TP, Stephens DA. Factors associated with a good response to lithium in aggressive mentally handicapped subjects. Prog Neuropsychopharmacol Biol Psychiatry 1984;8:751–5.
Ursano JR, Bell C, Eth S, Friedman M, Norwood A, Pfefferbaum B, et al. Practice guideline for the treatment of patients with acute stress disorder and posttraumatic stress disorder. Am J Psychiatry 2004;161:S3–S31.
US Department of Health and Human Services. Depression guideline panel. Clinical practice guideline No 5: depression in primary care, Vol 2: treatment of major depression. Rockvile: AHCPR Publications; 1993. p. 71–123.
van der Kolk BA, Greenberg MS, Orr SP, Pitman RK. Endogenous opioids, stress induced analgesia, and posttraumatic stress disorder. Psychopharmacol Bull 1989;25: 417–21.
van der Kolk BA, Dreyfuss D, Michaels M, Shera D, Berkowitz R, Fisler R, et al. Fluoxetine in posttraumatic stress disorder. J Clin Psychiatry 1994;55:517–22.
Watson CG, Juba MP, Manifold V, Kucala T, Anderson PE. The PTSD interview: rationale, description, reliability, and concurrent validity of a DSM-III-based technique. J Clin Psychol 1991;47:179–88.
Weathers FW, Litz BT, Herman DS, Huska JA, Keane TM. The PTSD Checklist (PCL): reliability, validity, and diagnostic utility. Paper present at the Annual Meeting of International Society for Traumatic Stress Studies; 1993.
Weiss DS, Marmar CR. The impact of event scale-revised. In: Wilson JP, Keane TM, editors. Assessing psychological trauma and PTSD: a practitioner's handbook. New York: Guilford Press; 1997. p. 399–411.
Westra HA, Stewart SH, Teehan M, Johl K, Dozois DJA, Hills T. Benzodiazepine use associated with decreased memory for psychoeducation material in cognitive behavioral therapy for panic disorder. Cogn Ther Res 2004;28:193–208.
Wheatley M, Plant J, Reader H, Brown G, Cahill C. Clozapine treatment of adolescents with posttraumatic stress disorder and psychotic symptoms. J Clin Psychopharmacol 2004;24:167–73.
Wolf ME, Alavi A, Mosnaim AD. Posttraumatic stress disorder in Vietnam veterans clinical and EEG findings—possible therapeutic effects of carbamazepine. Biol Psychiatry 1988;23:642–4.
Zohar J, Amital D, Miodownik C, Kotler M, Bleich A, Lane RM, et al. Double-blind placebo-controlled pilot study of sertraline in military veterans with posttraumatic stress disorder. J Clin Psychopharmacol 2002;22:190–5.