Pharmacotherapy for disordered sleep in post-traumatic stress disorder: a systematic review
Saskia van Liempta, Eric Vermettena,b, Elbert Geuzea,b and Herman G.M. Westenbergb

Sleep disorders, such as insomnia and nightmares, are common problems in post-traumatic stress disorder (PTSD), exert a strong negative influence on the quality of life and are a great challenge for clinical psychiatry. Several studies have reported on the efficacy of drugs for the treatment of PTSD-related sleep disorders. These studies have not been systematically reviewed. This is the first review on the effectiveness of sleep medication in PTSD.

We performed a Medline, EMBASE and Cochrane Library indexed search, using the keywords: PTSD, pharmacotherapy, therapy, sleep, nightmares, insomnia and review. From this database, English-language, human subject, data driven papers published after 1980 were selected. Forty eight articles are discussed. Open-label and case studies suggest efficacy for some antidepressants, anticonvulsants and atypical antipsychotics. Only a few placebo-controlled studies have been published. They show promising results for the atypical antipsychotic olanzapine, and the α1-adrenoceptor antagonist prazosin. In comparison to the incidence and impact of sleep complaints in PTSD, the pharmacotherapeutic armamentarium for PTSD-related sleep complaints remains poorly investigated. Some recent studies show promising results, especially for α1-adrenoceptor and 5-HT2 receptor antagonists. However, randomized controlled trials with larger populations need to be conducted. Int Clin Psychopharmacol 21:193–202 © 2006 Lippincott Williams & Wilkins.

Introduction
Post-traumatic stress disorder (PTSD) is a chronic and disabling disorder, characterized by specific symptoms that develop following exposure to trauma where the person’s response involves intense fear, helplessness or horror. Among the core symptoms of PTSD are re-experiencing the event, avoidance of stimuli, and persistent symptoms of increased arousal. In clinical presentation of symptoms, sleep complaints are frequently reported (Geuze and Vermetten, 2004). Sleep disturbances affect approximately 70% of PTSD patients (Ohayon and Shapiro, 2000), with frequent nightmares and anxiety dreams, frequent awakenings, difficulty falling asleep, decreased total sleep time and restless sleep as the most reported complaints (Dagan et al., 1991; Mellman et al., 1995c; Dow et al., 1996; Woodward et al., 1996; Mellman et al., 1997; Lavie et al., 1998; Ross et al., 1999; Engdahl et al., 2000; Woodward et al., 2000; Krakow et al., 2002; Neylan et al., 2003a,b; Breslau et al., 2004). A number of studies describe other alterations in sleep with unclear clinical importance. These alterations include less movement time, especially in patients with nightmares or co-morbid panic disorder (Woodward et al., 2002). Trauma-related nightmares were also associated with more wake after sleep time, whereas non-trauma-related nightmares were not (Woodward et al., 2000). Furthermore, elevated arousal thresholds during non-REM (NREM) and REM sleep have been described (Dagan et al., 1991; Lavie et al., 1998). In PTSD, more β-band power was reported during REM compared to NREM, and heart rate differences between REM and NREM were related to the amount of REM sleep (Woodward et al., 2000).

Sleep disturbances warrant special attention in the treatment of PTSD symptoms because sleep complaints are generally severe and may exist decades after the original trauma (Schreuder et al., 2000). The results from controlled polysomnographic studies are not unambiguous on altered sleep latency, sleep efficiency, number of arousals, total sleep time, percentage rapid eye movement (REM) and slow wave sleep (SWS), and sleep disturbed breathing (Ross et al., 1994; Mellman et al., 1995c; Dow et al., 1996; Woodward et al., 1996; Mellman et al., 1997; Lavie et al., 1998; Ross et al., 1999; Engdahl et al., 2000; Woodward et al., 2000; Krakow et al., 2002; Neylan et al., 2003a,b; Breslau et al., 2004). Objective criteria for impaired sleep in PTSD require further exploration to better understand the underlying mechanism, and to develop adequate therapeutic interventions for this severe clinical problem.
From a theoretical perspective, several drugs may be useful in the treatment of disordered sleep in PTSD. Based on the reported neurobiological abnormalities in PTSD, it be may argued that altered activity of noradrenaline, serotonin and gamma amino-butyric acid (GABA) may play a role in the observed sleep problems. Noradrenaline dysfunction has been reported in PTSD by several investigators (Southwick et al., 1999; Charney et al., 1993; Vermetten and Bremner, 2002; Charney, 2004). One study found increased sympathetic activation during REM sleep in the acute aftermath of trauma in subjects who went on to develop PTSD (Mellman et al., 2004). Additionally, an abnormal increase in methoxyhydroxyphenylglycol (the major noradrenaline metabolite) levels during night has been observed in PTSD, which was negatively related to total sleep time (Mellman et al., 1995c). Preclinical studies show that noradrenaline is important for arousal regulation during sleep and for the regulation of REM sleep (Ouyang et al., 2004). Moreover, noradrenaline promotes wakefulness under stressful conditions (Hunsley and Palmiter, 2004). Agents inhibiting noradrenergic activity in the brain may thus alleviate sleep complaints. Furthermore, selective serotonin reuptake inhibitors (SSRIs) are effective for PTSD symptoms and 5-HT2 receptors are supposed to play a critical role in SWS regulation (Idzikowski et al., 1991). In depression, 5-HT2 receptor antagonists have shown to be effective for sleep complaints (Sharpley et al., 1994). Possibly, agents with 5-HT2 receptor blocking properties may also have a positive influence on sleep in PTSD.

Activation of GABAA receptors plays a crucial role in the initiation and maintenance of NREM sleep (Lancel, 1999). Low plasma GABA levels have been found in patients who later develop PTSD (Vaiva et al., 2004). Moreover, decreased benzodiazepine receptor binding has been found in the prefrontal cortex of PTSD patients (Bremner et al., 2000). In addition, decreased density of platelet benzodiazepine receptors has been observed in combat-related PTSD patients (Gavish et al., 1996). Thus, besides noradrenaline and serotonin, altered GABAergic activity may contribute to sleep disturbances in PTSD patients.

In the past two decades, several trials have been performed in which drugs were evaluated for their efficacy in the treatment of subjective sleep complaints in PTSD patients. Recently, some promising studies have been published that show new possibilities in the treatment of PTSD-related sleep complaints. The objective of this review is to provide an up-to-date overview of the literature on the pharmacotherapy of sleep disorders in PTSD, and to provide suggestions for drug treatment and to formulate recommendations for future research.

Materials and methods

We performed a Medline, EMBASE and Cochrane Library Indexed search using the keywords: PTSD, pharmacotherapy, sleep, nightmares, insomnia and review. From this database English-language, human subject, data driven papers published after 1980 were selected. Articles were excluded if sleep was not evaluated and explicitly mentioned as a separate outcome measure. Forty-eight relevant articles were found. The first studies on the efficacy of pharmacotherapy for sleep disorders in PTSD were published between 1980 and 1990. The drugs studied were predominantly the tricyclic antidepressants (TCAs) and monoamine oxidase inhibitors (MAOIs). In the following decade (1990–2000), studies concentrated on the effect of SSRIs, anticonvulsants and benzodiazepines. More recently, the efficacy of (atypical) antipsychotics, the antidepressants nefazodone, trazodone and mirtazapine, and the adrenergic agents prazosin and clonidine, have been evaluated for their efficacy in disordered sleep in PTSD. Studies will be discussed according to their classification as TCAs, MAOIs, anxiolytics and anticonvulsants, SSRIs, other antidepressants, antipsychotics and other agents.

Results

Tricyclic antidepressants

TCAs are used as second line treatment in major depressive disorder (MDD). In some countries, such as the Netherlands, TCAs are also advised as second-line treatment for PTSD. TCAs are known to reduce REM sleep, increase REM latency, and to worsen sleep continuity in the first month after treatment (Wilson and Argyropoulos, 2005). Few studies report on the use of TCAs in PTSD-related sleep complaints. One small trial compared imipramine and chloral hydrate in the treatment of 25 pediatric burn patients with acute stress disorder (Robert et al., 1999). Eighty percent of all patients treated with imipramine for 1 week experienced symptom relief compared to 45% of patients treated with chloral hydrate. Eight of the responders no longer had nightmares, and a small sample of nine experienced significant relief of insomnia. In an open-label study with imipramine, in three out of the 12 PTSD patients, sleep improved after 1–2 months (Kinzie and Leung, 1989).

Monoamine oxidase inhibitors

MAOIs are mostly used in the treatment of therapy-resistant MDD. In PTSD, MAOIs have hardly been investigated. MAOIs suppress REM sleep in healthy volunteers and in MDD, whereas sleep continuity does not change (Wilson and Argyropoulos, 2005). Hogben and Cornfield (1981) reported on five veterans with PTSD treated with phenelzine in doses ranging from 45–75 mg. Remarkably, patients stopped having nightmares after 5 days to 1 month of medication. In one open-label study, recurrent dreams and sleep disturbance improved following treatment with phenelzine in 10 PTSD patients.
PTSD patients (Neal et al., 1997).

**Anxiolytics and anticonvulsants**

For many years, benzodiazepines have been frequently used for the treatment of insomnia, including PTSD-related sleep complaints. Effects on sleep architecture include reduced SWS, reduced REM sleep, and increased sleep continuity (Parrino and Terzano, 1996). In a recent single-blind, placebo-controlled cross-over study, treatment of subjective sleep disturbances with the benzodiazepine clonazepam was evaluated in six combat-related PTSD patients (Cates et al., 2004). Each patient received clonazepam and placebo for 2 weeks, with no effect on sleep complaints during clonazepam treatment. Four case reports demonstrated that temazepam improved symptoms of acute stress, including disturbed sleep (Mellman et al., 1998). A subsequent placebo-controlled trial with temazepam in the acute aftermath of trauma revealed that subjective sleep improved in the temazepam group, but this effect was not maintained when treatment was discontinued after 7 days (Mellman et al., 2002). Moreover, temazepam was not superior to placebo in preventing PTSD symptoms. Three case studies in combat-related PTSD were reported in which insomnia and other PTSD symptoms improved with the anxiolytic buspirone (Wells et al., 1991). Case reports have suggested efficacy for zolpidem and tiagabine, both non-benzodiazepine GABAergic hypnotics, in the treatment of insomnia and nightmares in PTSD (Dieperink and Drogemuller, 1999; Taylor, 2003).

Anticonvulsants are a recent addition for treatment of disordered sleep in PTSD. Gabapentin is an anticonvulsant, which increases SWS (Legros and Bazil, 2003). In a retrospective open-label study with gabapentin addition to the standard treatment in 30 PTSD patients, an improvement for the duration of sleep was seen in 77% of the patients, and a decrease in the frequency of nightmares was noted (Hamner et al., 2001). Topiramate is another anticonvulsant that has been tested. Effects on sleep are unknown. One case study and two open-label studies suggest effect of topiramate on complaints of poor sleep in PTSD patients (Berlant, 2001; Berlant and van Kammen, 2002) (Table 1).

**Selective serotonin reuptake inhibitors**

SSRIs are commonly used in the treatment of PTSD symptoms. SSRIs improve the treatment of insomnia and nightmares in PTSD patients. In a retrospective open-label study with gabapentin addition to the standard treatment in 30 PTSD patients, an improvement for the duration of sleep was seen in 77% of the patients, and a decrease in the frequency of nightmares was noted (Hamner et al., 2001). Topiramate is another anticonvulsant that has been tested. Effects on sleep are unknown. One case study and two open-label studies suggest effect of topiramate on complaints of poor sleep in PTSD patients (Berlant, 2001; Berlant and van Kammen, 2002) (Table 1).

Other antidepressants

Other antidepressants have not yet been tested as extensively as SSRIs in the treatment of PTSD. Nefazodone, trazodone and mirtazapine have been examined for the treatment of sleep disturbances in PTSD because their effect has been proven in treating disordered sleep in other psychiatric disorders such as MDD (Nierenberg et al., 1994; Rush et al., 1998; Manber et al., 2003; Winokur et al., 2003).

In MDD and in healthy controls, nefazodone improves sleep continuity, without effects on REM sleep (Wilson and Argyropoulos, 2005). Nefazodone is a 5-HT1 receptor antagonist, and has a1-adrenoceptor blocking properties. Seven open-label studies on the effect of nefazodone in PTSD patients have been published (Hertzberg et al., 1998; Davidson et al., 1998; Mellman et al., 1999; Zisook et al., 2000; Gillen et al., 2001; Hertzberg et al., 2002; Neylan et al., 2003). A pooled analysis of these studies revealed significant improvement in sleep duration and reduction of nightmares (Fidalgo et al., 1999). A greater improvement was seen in patients with PTSD associated

Placebo-controlled trials have shown efficacy for paroxetine in the treatment of PTSD symptoms, including sleep disturbances. This was confirmed in a pooled analysis of three placebo-controlled studies (Stein et al., 2003). A placebo-controlled trial showed a significant decrease in ‘trouble sleeping’ after fluoxetine treatment, as measured by a self-administered questionnaire. However, the improvement was not significant, as measured by a structured interview. Fluoxetine did not have an effect on nightmares in this study (Meltzer-Brody et al., 2000) In two open-label studies, the effectiveness of fluvoxamine in the treatment of sleep complaints in combat-related PTSD has been evaluated. The first study showed no statistically significant decrease in insomnia and nightmares in 24 combat-related PTSD patients (De Boer et al., 1992). A large number of patients terminated this study prematurely, mainly due to gastrointestinal complaints. In another study, both sleep maintenance and sleep onset insomnia improved, although the effect was larger for sleep maintenance (Neylan et al., 2001). The largest effect was seen on the frequency of trauma-related dreams. Sertraline did not induce improvement in sleep quality compared to placebo (Davidson et al., 2001). In this relatively large trial (n = 208), sleep was evaluated as a secondary outcome measure. Insomnia as a side-effect occurred significantly more frequently in the sertraline group (35%) than in the placebo condition (22%).
Table 1 Anxiolytics and anticonvulsants in the treatment of disorder sleep in post-traumatic stress disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Type of trauma</th>
<th>No. of subjects</th>
<th>Nightmares</th>
<th>Insomnia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temazepam</td>
<td>Mellman et al. (1998)</td>
<td>Placebo-controlled</td>
<td>1 week</td>
<td>Civilian</td>
<td>4</td>
<td>NR</td>
<td>↓</td>
</tr>
<tr>
<td>Buspironone</td>
<td>Mellman et al. (2002)</td>
<td>Placebo-controlled</td>
<td>6 weeks</td>
<td>Civilian</td>
<td>22</td>
<td>NR</td>
<td>=</td>
</tr>
<tr>
<td>Zolpidem</td>
<td>Dieperink and Drogemuller (1999)</td>
<td>Case report</td>
<td>3 months to 1 year</td>
<td>Combat</td>
<td>3</td>
<td>↓</td>
<td></td>
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<tr>
<td>Tiagabine</td>
<td>Taylor (2003)</td>
<td>Case report</td>
<td>9 months</td>
<td>Combat</td>
<td>3</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Clonazepam</td>
<td>Cates et al. (2004)</td>
<td>Placebo-controlled</td>
<td>8 weeks</td>
<td>Civilian</td>
<td>7</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td>Gabapentin</td>
<td>Hammer et al. (2001)</td>
<td>Open-label</td>
<td>1–2 months</td>
<td>Combat</td>
<td>6</td>
<td>=</td>
<td></td>
</tr>
<tr>
<td>Topiramate</td>
<td>Berlant (2001)</td>
<td>Case report</td>
<td>1–5 months</td>
<td>Civilian</td>
<td>3</td>
<td>NR</td>
<td></td>
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<td>Berlant and van Kammen (2002)</td>
<td>Open-label</td>
<td>4 weeks</td>
<td>Civilian</td>
<td>35</td>
<td>NR</td>
<td></td>
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</tbody>
</table>

↓, Decreased; =, no change; NR, not reported.

with civilian trauma, in women, and in younger individuals. One group of authors evaluated long-term effects of nefazodone 4 years after a 12-week treatment period (Hertzberg et al., 2002). Compared to baseline (sleep quality before treatment 4 years earlier), total hours of sleep per night, and Pittsburg Sleep Quality Index (PSQI) scores were still significantly improved. However, compared to the results after 12 weeks of treatment, patients had less hours of sleep per night. All patients still met criteria for PTSD after 4 years.

Three of the open-label studies evaluated the efficacy of nefazodone by using both subjective and objective measures. In the study of Mellman et al. (1999), trauma-related nightmares and total sleep time did not improve significantly in the 11 patients studied, whereas overall PTSD symptom symptoms did. Polysomnographic (PSG) recordings obtained from four patients revealed a trend for a decrease in number of awakenings and arousals after treatment. In another study, 12 male combat veterans were included (Gillin et al., 2001). Patients reported less nightmares and sleep problems after treatment with nefazodone. However, no changes in sleep architecture were seen. Finally, Neylan et al. (2003a) assessed the effectiveness of nefazodone on both subjective and objective sleep quality in 10 male veterans for 12 weeks. Subjective sleep quality and ambulatory PSG were assessed at baseline and after 12 weeks. A significant improvement of insomnia complaints and a decrease in nightmares was seen. PSG showed a significant increase in total sleep time, sleep maintenance, and delta sleep after treatment with nefazodone.

Trazodone promotes sleep continuity and induces a decrease in REM sleep (Wilson and Argyropoulos, 2005). Trazodone blocks the 5-HT1A, 5-HT2, and 5-HT2 adrenoceptor. An open-label study with trazodone reported that sleep was the first symptom to improve in six patients with PTSD (Hertzberg et al., 1996). In a survey of 74 PTSD patients with sleep disturbances, trazodone was effective in decreasing nightmares in 72% of the 60 patients who tolerated the medication (Warner et al., 2001). Ninety-two percent of the patients considered trazodone effective with regard to sleep-onset, and 78% reported improvement in sleep maintenance. Priapism was reported as a side-effect in 12% of cases.

Mirtazapine is a 5-HT2 receptor antagonist with H1 and 5-HT2 receptor antagonistic properties. It improves sleep continuity in MDD and in healthy controls (Wilson and Argyropoulos, 2005). Lewis et al. (2002) reported their preliminary results on the effectiveness of mirtazapine. Mirtazapine was prescribed in more than 300 refugees with trauma-related nightmares. It was estimated that 75% of the patients experienced a reduction in the frequency and intensity of nightmares (Table 2).

### Antipsychotics

The utility of antipsychotics in PTSD patients has been recently reviewed by Ahearn et al. (2003). In healthy subjects, olanzapine administration increases sleep continuity and enhances SWS (Sharpley et al., 2000). Additionally, olanzapine improves sleep continuity and increases SWS in patients receiving SSRI treatment (Sharpley et al., 2005). The use of olanzapine in the treatment of sleep complaints in PTSD patients has been evaluated in one series of case reports and in one placebo-controlled study. The case reports show that addition of olanzapine to SSRIs is useful in treating nightmares and insomnia in patients with combat-related PTSD (Jakovljevic et al., 2003). A randomized placebo-controlled trial confirmed these findings (Stein et al., 2002). Nineteen patients with PTSD were included in this double-blind, placebo-controlled study in which olanzapine was added to SSRI treatment. Although this study showed that olanzapine addition was associated with a statistically significant reduction of nightmares and improvement of insomnia, no significant global clinical improvement in PTSD symptoms was seen compared to placebo. Olanzapine use was associated with 13lb weight gain over 8 weeks versus 3lb weight loss in the placebo group. In a recent open-label study, quetiapine alleviated nightmares and insomnia complaints in 20 combat-related PTSD patients (Robert et al., 2005). Levomepromazine was studied in a 4-week open-label study in 21 patients, and robust improvement was seen on nightmares and complaints of insomnia (Aukst-Margetic et al., 2004). Anecdotal reports show a possible efficacy for the atypical antipsychotic risperidone and thioridazine (Dillard et al., 1993; Leyba and Wampler, 1998) (Table 3).

### Other drugs

Prazosin, a selective 5-HT2 adrenoceptor antagonist, is known for its antihypertensive properties, and is not widely used
in the treatment of PTSD. Sleep has not been evaluated in humans after prazosin administration. In preclinical studies, the duration of REM sleep per episode was blocked by prazosin in the rat (Kleinlogel, 1989; Mallick et al., 2005). In other studies, prazosin facilitated REM sleep in cats (Hilakivi and Leppavuori, 1984) and in rats (Makela and Hilakivi, 1986). When combat-related PTSD patients were treated with prazosin for their complaints related to benign prostate hypertrophy, the patients reported an unexpected reduction in REM sleep per episode. The observation prompted the investigators to conduct an open-label feasibility trial with prazosin in five civilian PTSD patients (Taylor and Raskind, 2002) and another study in nine older men with chronic PTSD (Peskind et al., 2003). In these studies, nightmares and insomnia complaints improved. Optimal doses of prazosin ranged from 1 to 4 mg/day. Furthermore, a retrospective chart study was performed, which analysed data from 59 combat veterans with severe combat-related nightmares, to whom prazosin had been prescribed (Raskind et al., 2002). The mean scores for recurrent distressing dreams improved significantly in 36 of the patients who completed at least 8 weeks of treatment. The mean maximum dose in these 36 patients was 9.6 mg per day. There were no serious adverse events attributable to prazosin. Subsequently, a small placebo-controlled cross-over study with prazosin was conducted (Raskind et al., 2003). Ten Vietnam veterans with chronic PTSD received prazosin and placebo for 9 weeks, with a wash-out period of 2 weeks in between. Prazosin was superior to placebo for treating difficulties in falling and staying asleep, for global PTSD severity, and for recurrent distressing dreams. The mean dosage of prazosin was 9.5 mg/day. Seven patients used other psychoactive drugs at the time of the study. Orthostatic hypotension was reported as a transient side-effect.
Clonidine, a α2-adrenoceptor agonist, increased the amount of REM sleep and decreased the amount NREM sleep at low-dosage in healthy subjects (Miyazaki et al., 2004). By contrast, medium-dose clonidine significantly decreased REM and increased NREM. A relatively high dose of clonidine (0.3 mg/day) was effective for subjective sleep complaints in four patients (Kinzie et al., 1994). PSG showed REM suppression after administration of clonidine; however, sleep continuity did not improve. In another study, clonidine was added to imipramine in nine patients (Kinzie and Leung, 1989). After 12–19 months of treatment, insomnia improved in six, and nightmares improved in seven out of nine patients.

Cyproheptadine, a 5-HT2 receptor antagonist, is commonly prescribed in patients with allergic conditions. Furthermore, it is known for its sleep-promoting properties. Cyproheptadine administration is followed by a reduction in REM sleep in healthy volunteers and MDD (Sharpley et al., 1990). Several case studies have reported that cyproheptadine is efficacious in treating nightmares in PTSD (Harsch, 1986; Brophy, 1991; Rijnders et al., 2000). In a retrospective study, nine patients with PTSD who were treated with cyproheptadine also reported remission of nightmares (Gupta et al., 1998). However, a double-blind randomized, placebo-controlled trial in 69 patients with combat-related PTSD could not confirm these findings (Jacobs-Rebhun et al., 2000). After 2 weeks of treatment, no improvement in sleep-related symptoms was seen in comparison to placebo (Table 4).

**Table 4  Prazosin, clonidine and cyproheptadine in the treatment of disordered sleep in PTSD**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Reference</th>
<th>Study design</th>
<th>Follow-up</th>
<th>Type of trauma</th>
<th>No. of subjects</th>
<th>Nightmares</th>
<th>Insomnia</th>
<th>EEG</th>
</tr>
</thead>
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<tr>
<td>Prazosin</td>
<td>Raskind et al. (2000)</td>
<td>Case report</td>
<td>8 weeks</td>
<td>Combat</td>
<td>4</td>
<td>↓</td>
<td>↓</td>
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<tr>
<td></td>
<td>Raskind et al. (2002)</td>
<td>Open-label (retrospective)</td>
<td>8 weeks</td>
<td>Combat</td>
<td>59</td>
<td>↓</td>
<td>↓</td>
<td>NR</td>
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<td>Peskind et al. (2003)</td>
<td>Open-label</td>
<td>8 weeks</td>
<td>Combat/holocaust</td>
<td>9</td>
<td>↓</td>
<td>↓</td>
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<td></td>
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<td>Raskind et al. (2003)</td>
<td>Placebo-controlled</td>
<td>9 weeks</td>
<td>Combat</td>
<td>10</td>
<td>↓</td>
<td>↓</td>
<td></td>
<td></td>
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<tr>
<td>Clonidine</td>
<td>Kinzie and Leung (1989)</td>
<td>Open-label</td>
<td>12–19 months</td>
<td>War trauma</td>
<td>9</td>
<td>↓</td>
<td>↓</td>
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<td></td>
<td>Kinzie et al. (1994)</td>
<td>Case report</td>
<td>2 weeks</td>
<td>War trauma</td>
<td>4</td>
<td>↓</td>
<td>↓</td>
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<td></td>
<td>Gupta et al. (1998)</td>
<td>Case report</td>
<td>1 month to 1 year</td>
<td>Civilian/combat</td>
<td>9</td>
<td>↓</td>
<td>↓</td>
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<td>Cyproheptadine</td>
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<td>Case report</td>
<td>NR</td>
<td>Combat</td>
<td>4</td>
<td>↓</td>
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<td>Rijnders et al. (2000)</td>
<td>Case report</td>
<td>1 week</td>
<td>Civilian</td>
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<td>↓</td>
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<td>Jacobs-Rebhun et al. (2000)</td>
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<td>Combat</td>
<td>69</td>
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↓, Decreased; =, no change; NR, not reported.

Cyproheptadine, a 5-HT2 receptor antagonist, is commonly prescribed in patients with allergic conditions. Furthermore, it is known for its sleep-promoting properties. Cyproheptadine administration is followed by a reduction in REM sleep in healthy volunteers and MDD (Sharpley et al., 1990). Several case studies have reported that cyproheptadine is efficacious in treating nightmares in PTSD (Harsch, 1986; Brophy, 1991; Rijnders et al., 2000). In a retrospective study, nine patients with PTSD who were treated with cyproheptadine also reported remission of nightmares (Gupta et al., 1998). However, a double-blind randomized, placebo-controlled trial in 69 patients with combat-related PTSD could not confirm these findings (Jacobs-Rebhun et al., 2000). After 2 weeks of treatment, no improvement in sleep-related symptoms was seen in comparison to placebo (Table 4).

**Discussion**

To date, an insufficient number of controlled studies are published to formulate evidence-based guidelines. Additionally, several studies have methodological limitations, such as small group sizes and heterogenic samples. Drawing on the available data, it can be concluded that TCAs are not advised as first-line treatment for PTSD-related sleep disturbances because evidence is scarce and TCAs are known to worsen sleep continuity. MAOIs are also not advised as first-line treatment for PTSD-related sleep complaints, given their potential for serious side-effects and the limited evidence for efficacy in PTSD. However, because MAOIs can completely suppress REM sleep, they may be considered in individual cases of therapy resistant nightmares. Even though benzodiazepines are the most widely prescribed sleep medication, their effects on sleep disturbances in PTSD are generally disappointing. Clinicians should be careful in prescribing benzodiazepines because dependence and tolerance easily occur, even after short-term usage. Furthermore, benzodiazepines are contra-indicated in patients with a comorbid alcohol problem, which is especially frequently seen in combat-related PTSD patients. Sertraline treatment did not induce improvement in sleep; moreover, sertraline worsened sleep complaints in PTSD (Stein et al., 2002). Studies investigating the effect of paroxetine showed a different effect on sleep disturbances in PTSD compared to studies with sertraline (Davidson et al., 2001; Stein et al., 2003). Paroxetine has additional anticholinergic properties, and may be capable of suppressing REM sleep more strongly (Rao et al., 2004). Alternatively, sleep complaints may have decreased after paroxetine treatment due to the overall improvement of PTSD symptoms. In general, after SSRI treatment, residual sleep complaints are likely to occur. Other therapeutic options have to be considered in the case of persistent sleep complaints. For example, nefazodone, trazodone and mirtazapine may have therapeutic potential in the treatment of sleep disorders in PTSD patients by virtue of their noradrenergic and 5HT2 receptor-blocking properties. Furthermore, there is limited but promising evidence from a small placebo controlled study for treating sleep disorders in PTSD with olanzapine as add-on therapy. Possibly, other typical and atypical antipsychotics, particularly those that block the 5-HT2 receptors, are also effective. Weight gain is the most worrisome side-effect of olanzapine. Furthermore, as in the treatment of schizophrenia, development of the metabolic syndrome in chronic atypical antipsychotic treatment in PTSD is a major concern.
The usefulness of prazosin for treating disordered sleep in PTSD appears to be promising. It is relatively well evaluated in a controlled trial, and few side-effects have been reported. Based on known pharmacological properties, and supported by some open-label studies, clonidine and cyproheptadine may be useful as well. Cyproheptadine was not effective in a relatively large controlled trial in chronic PTSD, but 2 weeks of treatment may be too short to induce improvement in chronic disordered sleep.

These results should be reconsidered in placebo-controlled trials. Furthermore, drugs should be evaluated with PSG to understand the effect on sleep architecture in PTSD. Several confounding factors must be taken into account regarding these preliminary results. The placebo effect observed in the only large placebo-controlled trial conducted to date was large (Davidson et al., 2001). Thus, improvement in open-label studies may be due to placebo effect. Furthermore, samples differed between studies with respect to type of trauma, age, and concurrent treatment, which limits the ability to generalize results. Also, comorbidity, such as major depression, panic disorder and alcohol abuse, was commonly seen in most, but not all studies. Panic disorder has been shown to improve in open-label studies may be due to placebo effect. Furthermore, samples differed between studies with respect to type of trauma, age, and concurrent treatment, which limits the ability to generalize results. Also, comorbidity, such as major depression, panic disorder and alcohol abuse, was commonly seen in most, but not all studies. Panic disorder has been shown to influence subjective sleep in PTSD (Leskin et al., 2002), and to influence frequency of nightmares and movement during sleep (Woodward et al., 2002). MDD as comorbid disorder has been shown to alter sleep functions in PTSD (Woodward et al., 1996; Mellman et al., 1997). Possibly, the occurrence of comorbid disorders in PTSD influences response to medication. Finally, cyproheptadine, mirtazapine, nefazodone and olanzapine have sedating effects through their antihistaminergic properties, which may influence the subjective impression of sleep quality without necessarily treating underlying sleep disturbances. This finding is especially interesting in the context of the observed discrepancy between subjective and objective sleep quality in PTSD (Woodward et al., 1996; Dagan et al., 1997; Hurwitz et al., 1998; Breslau et al., 2004). Subjective complaints may improve without objective sleep quality being disturbed in the first place. In two of the three studies that correlated objective and subjective disturbances before and after nefazodone treatment, the improvement of objective and subjective sleep was not in agreement. Subjective improvement and an increase in delta sleep, total sleep time, and a decrease in number of awakenings was seen in 10 patients in only one study. This study may be more reliable because ambulatory PSG at the patients' homes was used. In all studies showing a discrepancy between subjective and objective sleep parameters in PTSD, sleep was recorded in a sleep laboratory, possibly giving a false view on the disturbed sleep in the homes of patients.

Another explanation for the discrepancy of subjective sleep and objective sleep disturbances in PTSD is that sleep disturbances may be subtle and not detectable by standard visual PSG analyses. This is suggested by two studies that found disturbances in quantitative delta activity, with a normal amount of SWS (Woodward et al., 2002; Neylan et al., 2003a). Similarly, in 'sleep state misperception insomnia' or 'subjective insomnia', more subtle differences in EEG spectral activity were seen compared to subjects with normal sleep, whereas sleep architecture was normal according to PSG recordings (Krystal et al., 2002). Another study reported increased oxygen use during sleep in patients with subjective insomnia (Bonnet and Arand, 1997). Thus, even in the absence of disturbed sleep according to PSG, sleep may be disturbed in more subtle and yet to be explored ways. Subsequently (pharmacotherapy) for sleep complaints may still be warranted.

Interestingly, PTSD-related nightmares were associated with physical sleep disorders in several studies. Patients with a history of sleep apnoeas reported nightmares more frequently (De Groen et al., 1993). Furthermore, a reduction in nightmares was observed following treatment for sleep apnoeas with continuous positive airway pressure. Several hypotheses may explain this finding. Hypercapnia can induce anxiety in predisposed subjects (Griez et al., 1987). Furthermore, disorientation and confusion during arousal may contribute to the occurrence of nightmares after obstructive sleep apnoeas in PTSD patients. It has also been suggested that undiagnosed physical sleep disorders may exacerbate PTSD symptoms through chronic sleep fragmentation. Polysomnographic studies are warranted to further characterize the relationship between sleep apnoeas, the occurrence of nightmares and PTSD severity.

Prazosin alleviates nightmare and insomnia complaints, which contributes to the hypotheses of increased noradrenergic activity in PTSD-related sleep disturbances. Olanzapine, quetiapine, nefazodone and trazodone share α1-adrenoceptor blocking properties with prazosin, which may explain their efficacy in this respect. Furthermore, nefazodone, mirtazapine, trazodone and olanzapine, all have 5-HT2 receptor blocking properties, which also may explain their efficacy in sleep disorders because 5-HT2 receptors are implicated in sleep regulation. However, cyproheptadine, a non-selective 5-HT2 receptor antagonist, did not improve sleep after 2 weeks of treatment in a placebo controlled trial in 70 chronic combat-related PTSD patients. Most agents with positive effects are known to reduce REM sleep in MDD and healthy controls (nefazodone, trazodone, cyproheptadine, prazosine, clonidine, MAOIs, TCAs). Three controlled PSG studies in PTSD reported an elevated REM percentage of sleep (Ross et al., 1994, 1999; Engdahl et al., 2000). Whether the response is related to a decrease in REM sleep needs to be examined further.

In conclusion, from this review, α1-adrenoceptor antagonists and 5-HT2 receptor antagonists appear to be
promising in the treatment of PTSD-related sleep complaints. To further develop adequate therapeutic interventions, large randomized, placebo-controlled studies need to be performed. Objective parameters for insomnia and trauma-related nightmares need to be identified for understanding the underlying mechanisms of disturbed sleep in PTSD, and for evaluating therapy.

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References


