

Treatment of posttraumatic stress disorder - related nightmares and other sleep disturbances with risperidone in combat veterans and victims of domestic and childhood abuse

An overview of the literature

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Sleep disturbances including nightmares are often reported as hallmark of posttraumatic stress disorder (PTSD). The literature related to the pharmacological treatment of PTSD-related nightmares is sparse and inconclusive. After reviewing the literature it was obvious that currently a limited data on studies supporting the use of antipsychotic medications for the treatment of PTSD are published. Moreover, even more limited scientific evidence is now available to formulate evidence-based guidelines for the treatment of PTSD-related nightmares which are often reported as the most intrusive and disruptive symptom. Objective for this study is to review comprehensively the current research literature which reflects use of antipsychotic medication risperidone for the treatment of PTSD-related nightmares of different etiology.

Keywords: Posttraumatic stress disorder, nightmares, Risperidone.

Introduction

Nightmares and insomnia are considered to be one of the core symptoms of PTSD (Ross et al., 1989). DSM-IV-TR (American Psychiatric Association 2000) criteria for PTSD include 2 types of sleep disturbances: the first one is recurrent nightmares, listed in re-experiencing cluster (Criterion B), and the second one is sleep continuity disturbances, frequently caused by posttraumatic dreams, listed in the hyper-arousal cluster (Criterion D) (DSM-IV-TR, 2000).

Subjective reports of sleep abnormalities among combat veterans with PTSD revealed that 44-90% of patients reported having difficulties falling and staying asleep (Mellman et al., 1995), and 52-87% suffer from recurrent nightmares (Inman et al., 1990).

De Fazio et al. (1975) and Van Der Kolk et al. (1980), indicated that more than 60% of Vietnam combat veterans had one or more nightmares per month. Repetitive dreams reflecting traumatic military experiences of wartime or captivity events were reported by 80% of the war prisoners. The frequency of these frightening dreams remained unchanged in 39%, decreased in 30%, and increased in 17% of veterans with prolonged captivity and combat exposure (Guerrero and Crocq, 1994).

Neylan et al. (1998), demonstrated that in majority of cases the exposure to combat was substantially correlated with frequency of PTSD-related nightmares, although the presence

of PTSD itself was not always significantly related to severity of experienced traumatic military event (Mellman et al., 1995; Woodward et al., 2000). Patients with severe, chronic combat-related PTSD were much more prone to have recurrent trauma-related nightmares (Woodward et al., 2000).

Nightmares, which are common and very disturbing form of sleep disorders in patients with PTSD, have tremendous impact on their social, occupational, personal, and marital functioning (Chambers and Belicki, 1998).

Methods

Our literature review, using PUB MED database, resulted in finding 11 positive case reports, 5 randomized double-blind clinical studies, and 3 open trials, which have been demonstrating clinically positive results of Risperidone treatment for PTSD and related sleep disturbances, including nightmares (Bartzokis et al., 2005; Hammer et al., 2003; Monnelly and Ciraulo, 1999; 2003; Padala et al., 2006; Reich et al., 2004; Leyba, 1998; Eidelman et al., 2000; Krashin and Oats, 1999; David et al., 2003; 2006; Kozaric-Kovacic et al., 2005).

TABLE 1. RISPERIDONE USE IN PTSD

Reference	Number of patients	Study type	Trauma	Treatment mg/day	Additional medications(mg/day)	Results
1. Bartzokis et al., (2001)	48	16-weeks; double-blind placebo-controlled	Combat veterans	Risperidone 3 mg QHS	All types of antidepressants	Improved CAPS; HAMD; HAMA, PANSS
2. David et al., (2003)	16	12 –weeks; open trial	Combat, partially responsive	Risperidone (mean 2.5mg)	Existing medications	Decreased CAPS-B; PANSS; CGI
3. David et Al., (2006)	20	12 weeks; pilot open-label, flexible dose trial	Vietnam male combat veterans	Risperidone 1-3 mg (mean 2.3)	Antidepressants 100% Mood stabilizers 35% Anxiolytics 41%	Decreased CAPS total, CAPS B-2; CAPS D-1; PSQI total; Improvement in overall PTSD symptoms and sleep variables
4. Hamner et al., (2003)	37	5 weeks; randomized, double-blind, placebo-controlled	Combat with psychotic symptoms	Risperidone 1-6 mg (mean 2.5mg)	Existing medications. mainly antidepressants	Decreased PANSS; CAPS-B.
5. Monnelly et al., (2003)	15	6 weeks; randomized, double-blind, placebo-controlled	Combat	Risperidone 0.5-2 mg (mean 0.57)	Existing medications, mainly antidepressants	Decreased OAS-M irritability; PCL-M cluster B; PCL- M total
6. Kozaric et al (2005)	26	3-6 weeks; open trial	Combat	2-4 mg (mean 3.46)	Risperidone monotherapy	Decreased PANS; PTSD-I; CGI-S.
7. Eidelman et al., (2000)	4	Case report	Physical trauma	Risperidone 1 mg BID	None	Clinically improved.
			Physical trauma	Risperidone 1 mg BID	None	Clinically improved.
			Physical trauma	Risperidone 2 mg QHS	None	Clinically improved.
			Physical trauma	Risperidone	Citalopram 30 mg	Clinically improved.

TABLE 1. RISPERIDONE USE IN PTSD

Reference	Number of patients	Study type	Trauma	Treatment mg/day	Additional medications(mg/day)	Results
8. Leyba et al., (1998)	4	Case report	trauma	5 mg QHS		
			Combat	Risperidone 1 mg BID	Valproate 750 mg, Clonazepam 1 mg.	Decreased flashbacks.
			Combat	Risperidone 1 mg BID	Fluoxetine 20 mg, Clonazepam 1 mg.	Decreased nightmares.
			Combat	Risperidone 1 mg BID	Paroxetine 20 mg, Clonazepam 1.5 mg.	Decreased nightmares.
			Combat	Risperidone 1 mg AM, 2 mg QHS.	Paroxetine 20 mg, Valproate 1250 mg,	Decreased nightmares and flashbacks.
9. Krashin et al., (1999)	2	Case report	Physical trauma Child abuse	Risperidone 5mg BID Risperidone	Trazodone, Venlafaxine, Valproate,	Decreased flashbacks. Decreased intrusive
10. Monnelly et al., (1999)	1	Case report	Combat	Risperidone 1 mg Qdaily	Paroxetine 20 mg, Diazepam 10 mg QID	Decrease in irritability and aggression.
11. Reich et al., (2004)	21	8 weeks; randomized, double-blind, placebo-controlled	Adult women with chronic PTSD related to childhood physical, sexual, verbal, emotional abuse	Risperidone 0.5-8 mg/day	Other antipsychotics, SSRI, TCA, Benzodiazepines	Decreased CAPS-2 total score; Decreased intrusive and hyperarousal subscale scores.
12. Padala et al., (2006)	20	12-weeks; double-blind, placebo-controlled	Adult women with PTSD related to sexual assault and domestic abuse	Risperidone 0.5-6mg/day (mean 2.62mg)	None	Statistically significant improvement in intrusive recollections, physiological distress, numbing, anhedonia, estrangement, avoidance of activities, hypervigilance, and increased startle

Note: CAPS = Clinical Administered PTSD Scale; HAMD = Hamilton Depression Scale; HAMA = Hamilton Anxiety Scale; PANS = Positive and Negative Symptom Scale; OAS-M = Overt Aggression Scale-Modified for outpatients; PCL-M = Patient Checklist for PTSD-Military version; CGI = Clinical Global Impression; PSQI = Pittsburgh Sleep Quality

Results

1. Bartzokis et al. (2005) in a 16 week double-blind placebo controlled study of 48 combat veterans, showed that adjunctive Risperidone treatment reduced many of the

PTSD symptoms, like hyperarousal, anxiety, as well as psychotic symptoms. Only 10% of patients were using Risperidone as a single agent. The Clinician Administered PTSD scale (CAPS) was used as the primary outcome measure. There was remarkable improvement in the overall CAPS score ($p=0.024$) and the hyperarousal subscale of the CAPS ($p=0.004$) for patients on Risperidone, comparing to placebo group (Table 1). Anxiety, which was measured using Hamilton Anxiety scale, and psychotic symptoms as measured by the Positive and Negative Symptom Scale, also demonstrated significant improvement with p -values of 0.002 and 0.009, respectively. For majority of patient in the study, Risperidone was generally well tolerated, and only few veterans discontinued the study due to side-effects.

2. Hamner et al. (2003) in a 5 week randomized controlled trial of Risperidone for the treatment of 38 patients with reexperiencing symptoms of PTSD and psychotic symptoms, reported a superiority of adjunctive Risperidone (1-6 mg/day) over placebo in decreasing the global psychosis ($p < 0.05$) as measured by the Positive and Negative Symptom Scale, as well as marked reduction in the CAPS reexperiencing subscale. (Table 1).
3. Monnelly and Ciraulo (1999), in one case report showed notable improvement in aggression and irritability in combat Vietnam veteran after Risperidone (1mg) was used in addition to Paroxetine and Diazepam (Table 1).
4. Relatively small ($n = 15$) 6 weeks randomized double-blind placebo-controlled study by Monnelly et al. (2003), reported reduction in PTSD-related irritability and intrusive thoughts in veterans who were treated with 0.5-2 mg/day of Risperidone as an adjunctive agent to antidepressant treatment. (Table 1). Overt Aggression Scale-Modified for Outpatients irritability subscale (mean reduction of 2.0 vs. 1.0; $p = 0.04$) was used to demonstrate that Risperidone was superior to placebo in symptom improvement.
5. Padala et al. (2006) in a small pilot 12 weeks monotherapy, double-blind study demonstrated that Risperidone monotherapy was found to be better than placebo in reducing mean TOP-8 scores, mean CAPS scores, which reflected improvement in 1) intrusive recollections; 2) physiological distress; 3) numbing; 4) anhedonia; 5) estrangement; 6) avoidance of activities; 7) hypervigilance, and 8) increased startle after Risperidone treatment of adult females with PTSD related to domestic violence and sexual assault (Table 1).
6. Reich et al. (2004) in 8 weeks randomized double-blind placebo-controlled trial evaluated the effect of adjunctive Risperidone in adult women with history of childhood sexual, physical and emotional abuse, and revealed that Risperidone was superior to placebo in decreasing intrusive and hyperarousal symptoms of PTSD (Table 1). Decrease in mean CAPS scores in the Risperidone group versus placebo group (29.6 and 18.6 points respectively) was statistically significant ($p = 0.015$), as well as decrease in CAPS-D (-21.1 versus -6.3; $p = 0.006$). 75 % of patients treated on Risperidone, and 78% of patients on placebo have completed the study. Comparing to Risperidone treatment group, where 4 patients reported such side-effects as dry mouth, tremor, sedation, apathy, and poor concentration, in placebo group the only one subject reported to having sedation as an adverse effect. There was no statistically significant difference in prolactin level and weight changes.
7. Leyba (1998) in series of four case reports demonstrated that addition of Risperidone (2-3 mg/day) to the previous psychotropic treatment regimen, (which included various

combinations of mood stabilizers, antidepressants, and benzodiazepines), caused significant reduction of nightmares and flashbacks in all 4 veterans (Table1).

8. Eidelman et al. (2000) presented patients with acute stress disorder as a result of physical trauma, who were treated with Risperidone (Table 1). Among 4 patients, who all had several hyperarousal symptoms, three were admitted to have avoidance symptoms, numbing, and flashbacks of the traumatic event. One patient had auditory hallucinations. The patients were taking 0.5-2.0 mg of Risperidone per day. There was clinically notable symptom clusters improvement with Risperidone treatment in all 4 patients, three of which were using Risperidone as a monotherapy, and in one patient Risperidone was added to Citalopram.
9. Krashin and Oates (1999) used Risperidone as an adjunctive treatment to Trazodone and Venlafaxine in 2 patients (Table 1). In one case, a veteran who was experienced trauma in military training superimposed on childhood abuse, was complaining of intrusive thoughts and frequent flashbacks which were notably improved after treatment with Risperidone (6 mg/day). Another combat veteran with PTSD who suffered from intrusive thoughts obtained marked relief after addition of Risperidone (2 mg/day) to his current treatment (Lithium, Clonidine, Fluoxetine, Zolpidem).
10. David et al. (2003), in open-labeled trial showed, that among 16 combat veterans who completed 12 weeks of adjunctive Risperidone (mean 2.5 mg/day), 47 % were remarkably improved on the CGI scale ($p < 0.04$) (Table 1). Total CAPS scores as well as hyperarousal subscale scores (CAPS-D) revealed some improvement ($p = 0.09$ and $p = 0.06$). Significant improvement ($p = 0.01$) was noted in reexperiencing symptoms (CAPS-B). Among 16 veterans, participated in the study, 15 suffered from psychotic symptoms. Statistically significant ($p = 0.04$) improvement correlated with total PANSS scores and PANSS positive and negative subscale scores. EPS was reported only by one patient, the rest of the veterans tolerated Risperidone well.
11. In a pilot 12 weeks, open-label, flexible dose trial David et al. (2006), evaluated preliminary effect of adjunctive Risperidone on PTSD-related sleep disturbances (nightmares, sleep disruption). (Table 1). Among 20 male Vietnam combat veterans 17 completed 6 weeks of the trial. The severity of PTSD and sleep abnormalities were measured with the CAPS at base line, 6 weeks and 12 weeks. The sleep/dream diaries which patients completed for the three consecutive nights at base line and at 6 weeks, reflected changes in frequency of awakenings, trauma-related dreams, and nightmares. The mean max. dose of Risperidone was 2.3 ± 0.6 mg/day. Analysis of CAPS total, CAPS B-2; CAPS D-1 and sleep log ratings evidenced that adjunctive Risperidone treatment was associated with improvement in majority of PTSD symptoms, as well as PTSD-related sleep disturbances.
12. Dragiga Kozaric-Kovacic et al. (2005), in open trial studied twenty six psychotic male patients with PTSD who were using Risperidone for 6 weeks. After 3 and 6 weeks of treatment with Risperidone, veterans were evaluated to having remarkable improvement in PANSS, PTSD-I, and CGI-S with base line scores decline of 44%-70% (Table 1). Statistically significant ($p < 0.05$) reduction in total and subscale scores on avoidance, trauma reexperiencing, and in total and subscale scores on the in psychotic PTSD subjects ANOVAs revealed that total and subscale scores on positive, negative, general psychopathology, and supplementary items of the PANSS; total and subscale scores on, avoidance, on the PTSD-I; and total scores on the CGI-S was revealed using repeated measured Analysis of Variance and Tukey multiple

comparison test. Side effects, including sedation, anxiety, EPS, weight gain, were observed in patients during the course of the treatment.

Discussion

Literature review indicated that aside from using different classes of antidepressants, anticonvulsants, gabapentin, alpha 2-adrenergic receptor agonists, cyproheptadine, trazodone, opioid antagonists, benzodiazepines and other psychotropic medications for treatment of PTSD and PTSD-related sleep disturbances, atypical antipsychotics have been used with some frequency and success for more than the last 20 years (Eileen et al., 2004).

The exact mechanism by which atypical antipsychotic risperidone might ameliorate PTSD-related nightmares and other sleep disturbances is not clear. It has not only high antiserotonergic activity, achieved via 5-HT_{2A} and 5-HT₇ receptors antagonism, but also antidopaminergic D₂ activity, which theoretically may exert a key role in reducing anxiety and insomnia. Besides that, risperidone has relatively strong affinity towards α -1 and α -2 type adrenoceptors, which theoretically allows above receptors minimize sympathetic outflow with potential ability to reduce symptoms of hyper arousal in PTSD patients (Ahearn et al., 2003; Krystal and Davidson, 2007; Schotte et al., 1996). This unique pharmacologic properties permits risperidone to modify not only serotonergic, dopaminergic, and noradrenergic neurotransmission, but also attenuate dysfunction in prefrontal cortex and amygdala, thought to be dysregulated in PTSD-related sleep disturbances, including nightmares (Shin et al., 2005; Rasmusson and Charney, 1997).

Thus, it could be assumed that treatment of PTSD-related sleep disturbances with atypical antipsychotic risperidone may be beneficial in pharmacological management of core symptoms of PTSD-related sleep abnormalities.

Conclusion

According to the results of Risperidone treatment in combat veterans with PTSD presented in this review, there was significant reduction in PTSD symptoms including nightmares and other sleep disturbances.

There is very limited information related to the effect of Risperidone, specifically on nightmares and other PTSD-related sleep disturbances, currently available in Pub Med, and other sources.

Further studies (retrospective, or randomized, placebo-controlled, clinical trials) are warranted to investigate the efficacy of Risperidone in the treatment of nightmares and other PTSD related sleep disturbances.

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