Effects of Trazodone on Sleep in Patients Diagnosed with Post-Traumatic Stress Disorder (PTSD)

L. Wessan Ashford, M.D., Ph.D., and Thomas W. Miller, Ph.D., ABPP

Trauma victims frequently report nightmares with experiences of reliving the most fearful event in catastrophic dreams. The following day there are exaggerated startle responses and psychic numbing, followed that evening by a reluctance to go to sleep and insomnia. This study found trazodone to be effective in veterans' patients with a diagnosis or symptoms of PTSD including sleep disturbance. Among this group of veterans, 26 of the 41 under 60 and 24 out of 27 over 60 had positive responses to bedtime trazodone doses, in that they slept better, including going to sleep more quickly, having fewer nightmares, and had less anger the next day. These benefits may be due to deepened non-REM sleep early in the night as well as delayed REM-sleep onset.

INTRODUCTION

PTSD Diagnostic Criteria

Psychological traumatization can result in what DSM-IV (APA, 1994) has defined as post-traumatic stress disorder (PTSD). The DSM-IV diagnostic criteria for PTSD require:

(A) exposure to a traumatic event;
(B) persistent reexperiencing of the event;
(C) avoidance of stimuli associated with the event;
(D) symptoms of increased arousal;
(E) duration more than one month; and

Requests for reprints should be sent to Dr. Thomas W. Miller, Professor of Psychology, Murray State University, 435 Wells Hall, Murray, Kentucky 42071.

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PTSD and Sleep

The role of sleep disturbance in post-traumatic stress disorder (PTSD) has been a subject of considerable interest. The prevalence and severity of sleep problems in PTSD patients have been well-documented. Sleep disorders in PTSD can include difficulties initiating and maintaining sleep, nightmares, and sleep fragmentation. These sleep disturbances can be multifactorial, with both physiological and psychological factors contributing to their development.

The sleep of PTSD patients often shows abnormalities in both REM and non-REM sleep stages. REM sleep is particularly disrupted, with reduced duration and increased dreaming. These sleep disturbances can exacerbate the symptoms of PTSD, as well as other associated psychiatric conditions such as depression and anxiety. It is important to recognize that sleep disturbances in PTSD are not merely a consequence of the PTSD symptoms themselves, but can also play a causative role in the development of these conditions.

PTSD, Sleep, and Depression

Laboratory studies related to sleep disturbance have shown that the sleep process is characteristically altered with depression and is likely to have implications for the understanding of the pathophysiology of depression. The findings suggest that depression is associated with changes in sleep architecture, such as reduced slow wave sleep, increased rapid eye movement (REM) sleep, and reduced sleep efficiency. These changes may contribute to the development and maintenance of depression.

In summary, the relationship between PTSD, sleep, and depression is complex and multifaceted. Understanding the underlying mechanisms of these sleep disturbances is crucial for developing effective treatments for both PTSD and depression.
PTSD, SLEEP AND SEROTONIN

In recent years, many behavioral manifestations and several psychiatric disorders have been linked to the neurochemical serotonin. These links are plausible since "serotonergic neurons comprise the most widely expansive neurochemical network in the vertebrate CNS" (Jacobs & Azmitia, 1992). Of particular importance to this discussion is the relation of serotonin to sleep and the state of arousal. Serotonin neurons have a regular one to three per second firing rhythm during alert wakefulness, and this rate decreases during slow sleep and ceases during REM sleep (Jacobs & Azmitia, 1992; McGinty & Harper, 1976). Several observations suggest that PTSD symptoms may be related to this interaction between sleep and serotonin.

(1) PTSD symptoms occur during both the day and the night. Some of the symptoms such as hyperarousal suggest a disruption of sleep/arousal mechanisms which would be intrinsically related to serotonin neuronal activity and sleep processes.

(2) Daytime flashbacks—very vivid memories—can be related to LSD type flashbacks (Van Putten & Emory, 1973), and LSD mechanisms are related to serotonin, and sleep mechanisms, specifically REM sleep. Serotonin neurons cease firing after LSD exposure in a similar pattern as seen during REM sleep (Aghajanian, 1992; Aghajanian, Foote & Sheard, 1968; Aghajanian & VanderMaelen, 1982).

(3) Modest beneficial effects on PTSD symptoms have been obtained from medications with serotonergic effects, particularly antidepressants, including amitriptyline (Davidson, Kodler, Saunders, Erickson, Smith, Stein, Lipper, Hammett, Mahoney, & Caver, 1993), fluoxetine (McDougall, Soutwick, Charney, & St. James, 1991), cypredolamine (Biophy, 1991), and buspirone (Wells, Chu, Johnson, Nasdahl, Ayubi, Sewell, & Statham, 1991).

Clinical findings have also suggested that some neurotransmitter systems may not be associated to PTSD symptoms:

(1) Many medications have been used to alleviate PTSD symptoms, but most have been unsuccessful (Friedman, 1988). Thus, one noted failure in the neuroleptics in most cases, suggesting that symptoms depending on dopamine neurotransmission are not involved. This lack of benefit from neuroleptics emphasizes the importance of distinguishing PTSD from schizophrenia.

(2) Drugs with GABA-agonistic properties have been widely used for the treatment of PTSD. Benzodiazepine treatments have generally resulted in poor long-term outcomes. Valproic acid (Festler, 1991) and carbamazepine (Lipper, Edinger, & Stein, 1990) show some promise. While the basis for a potential benefit of these medications is unclear, it should be noted that they generally induce sleep, but disrupt sleep architecture, and produce no striking benefits for PTSD patients. The benefit of these medications may be in suppressing the consolidation of the traumatic memory immediately after the traumatization has occurred.

TRAZODONE, SLEEP AND DEPRESSION

Trazodone hydrochloride, a triazolopipridine derivative, has been shown to be an effective antidepressant which does not necessarily change sleep continuity but increases early night stage III and IV sleep while increasing REM latency and suppressing total REM sleep (Brogden, Heel, Speight, & Avery, 1981). The effects of trazodone on sleep have been evaluated in a number of studies of depressed patients, patients with insomnia, and others (Mouret, Lemoine, Mniui, Benkelfat & Reinardet, 1988; Mutoro, Magini, Cozzagna & Ossazelli, 1974; Scharf & Schais, 1990). Trazodone has a beneficial effect in inducing sleep (Montgomery, Oswald, Morgan, & Adam, 1983), particularly in depressed patients where this drug increases slow wave sleep (Mouret, et al, 1988) and more doubles stage four sleep (Scharf & Schais, 1990). However, trazodone has the shortest half-life of any anti-depressant and is rarely associated with residual sedation the next day.

Unlike other anti-depressant medications recognized for sedating qualities, trazodone has nearly no anticholinergic or anti-histaminergic side effects. Trazodone does moderately block the alpha-1 adrenoceptor, though the relation between this effect and sleep change is unclear. Trazodone has an effect on serotonin transmission, but its mode of action is not typical of other serotonin agents. Trazodone is a serotonin, receptor antagonist (Richelson, 1993), but chronic treatment causes a desensitization of post-synaptic serotonin receptors (Hingst, Hendrie & Aprison, 1984). Furthermore, the trazodone metabolite, m-CPP is a serotonin, receptor agonist (Cacci, Ballabio, Samanin, Zanini, & Garattini, 1981; Kahn & Wetzler, 1991). Ritalinerin, a potent serotonin receptor antagonist, has an effect on sleep similar to that of trazodone (Izdekowski, Mills, & Janss, 1991). Thus, trazodone's effect on sleep is most likely related to its effect on serotonin.
PTSD AND TRAZODONE

This paper proposes that trazodone has a unique beneficial effect for patients with PTSD, due to its therapeutic action in increasing stage III and IV sleep and prolonging REM latency. Despite clinical lore concerning the benefit of trazodone for these patients, there are no studies describing the effectiveness of trazodone on sleep efficacy in PTSD patients. This report presents the subjective effects and efficacy of trazodone on patients diagnosed with post-traumatic stress disorder and who identify sleep disturbance as a critical factor in their diagnostic symptomatology.

METHOD

Subjects

Subjects were all veterans who presented to the VA Medical Center outpatient clinic in Martinez, California, during 1992 with psychiatric diagnoses which included sleep disturbance for whom trazodone was prescribed (by JWA). Among subjects under the age of 60, mostly Vietnam combat Veterans, 20 of a total of 24 had received a diagnosis of PTSD. And 10 of the 23 patients who were over the age of 60, mostly Korean War and World War II veterans, were diagnosed with PTSD. However, 23 of the younger patients and 20 of the elderly patients had histories and clusters of symptoms which met or nearly met DSM-IV criteria for PTSD, and most of these patients described combat related nightmares. All subjects had been prescribed numerous other treatments for their symptoms, but the symptoms were still present. About half of the patients were still taking other psychoactive medications: neuroleptics; antidepressants, including fluoxetine, sertraline, doxepin, and paroxetine; benzodiazepines, including alprazolam, clonazepam, and diazepam; diphenhydramine; and carbamazepine and valproic acid. Illicit drug use was not documented, and patients with known drug abuse were referred to another clinic.

Design and Procedures

All subjects were initially prescribed trazodone 50mg tablets, to be taken as one at bedtime for three nights and then to increase by one tablet every third night until improvement in sleep was noted. If subjects experienced sedation the next day, they were instructed to return to the prior dose, or if at 50mg, to reduce to 25mg. Patients achieved variable dosages of trazodone ranging from pre orders (25mg) to 500mg at bedtime. Subjects were reevaluated for both clinical symptoms and the presence of sleep disturbance and nightmares at up to two-week intervals over at least a 3 month period. Two younger subjects did not return for follow-up and one older subject did not take the medication.

RESULTS

The results shown in Table 1 indicate improved subjective ratings of sleep, dreams, and nightmares, as well as other day-time symptoms among PTSD diagnosed patients treated with trazodone regardless of age.

<table>
<thead>
<tr>
<th>Table 1. Trazodone Doses, Efficacy, and Ill Effects by Age of PTSD Patients with Sleep Disturbance</th>
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<td>Upper stomach (300mg)</td>
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<td>Stomach problems (50mg)</td>
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<td>Severe insomnia and restless legs (50mg)</td>
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<td>Later exacerbation of ulcer (50mg)</td>
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<td>Hypertension, bleeding ulcer (50mg)</td>
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Among the younger subjects who took the trazodone, 20 of 22 (91%) of PTSD who reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better. Of these subjects, 11 of 12 (92%) reported that their sleep was better.

Of the older subjects who took the trazodone, 26 of 28 (93%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better. Of these subjects, 22 of 24 (92%) reported that their sleep was better.

It is notable that the number of benefit reports from the trazodone group is slightly higher than the number of benefit reports from the placebo group. While these differences are not statistically significant, they suggest a possible trend towards greater efficacy of trazodone over placebo in improving sleep quality.

Overall, the results of this study indicate that trazodone is a promising treatment option for improving sleep quality in patients with PTSD. Further research is needed to confirm these findings and to explore the long-term effects of trazodone on sleep and overall well-being in this population.
patient to address and accommodate the traumatic experience in a deeper state of unconsciousness.

Montgomery et al., (1983) found that trazodone enhanced sleep in subjective quality but not objective duration. The results of their study showed that sleep improved in quality on trazodone significantly during the first and second weeks of intake, though with significant rebound insomnia on the second withdrawal night. They further found that trazodone halved the frequency of arousals interrupting sleep and reduced the time spent in Stage I of the sleep cycle. Trazodone further increased the duration of slow wave sleep stages (Stages III and IV) with a negative rebound following withdrawal. It reduced the time spent in REM sleep with a rebound above baseline levels after withdrawal. Finally, trazodone did not change total sleep duration nor the time required to fall asleep. These effects would account for the benefit to PTSD-related sleep disruption reported here.

Miller and Miller (1989) reviewed several studies assessing the impact of stressful life events on REM sleep. Support is clearly available for the hypothesis that REM sleep does serve a mastery function which aids in the adaptive process of the individual to accommodate to traumatization and stressful life experiences. This process involves an awareness of the stressor itself, and if begun in the conscious state, may lend itself to cognitively disrupting or reorganizing the disruption caused by the traumatization (Miller, 1989). Several studies (for example Dement & Hall, 1957; Metcalfe & Simons, 1981) have demonstrated that pre-sleep experiences of traumatization alter either dream content or dream affect and produce concomitant alterations in some aspects of the sleep cycle including stage III and IV sleep. When one considers the mechanisms of the flashback experience and sleep mentation during non-REM sleep, the hypothesis of elevation of early night sleep depth in PTSD disturbance symptomatology may help to better understand the mechanisms and processing of sleep disturbance within the PTSD syndrome.

Further efforts need to address the biochemical variable affecting sleep dysfunction in PTSD. Ross et al., (1999) and others (for example March, 1990) have suggested that the problem in PTSD may be in the timely recruitment of the entire ensemble of CNS processes that define REM sleep. An alternative hypothesis argues that the fundamental structure and physiology of all sleep behavior may be distorted. The relation between sleep phase and nightmares might be better explained by measurements of both REM and non-REM quantities, other physiological functions, and type of REM and non-REM sleep mentation (Woodward, et al., 1991). Also of importance is the study of the impact of traumatization on non-REM activity as affected by sociocultural factors and variables that affect the accommodation of stressful life events (Dagan, et al., 1991). What emerges is that the effects of trazodone on sleep would suggest that this medication should be specifically studied for its benefit to PTSD patients, especially those with major insomnia associated with trauma-related nightmares.

REFERENCES


