Survey on the Usefulness of Trazodone in Patients with PTSD with Insomnia or Nightmares

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Background: Trazodone is commonly used in the treatment of insonmia and nightmares in patients with PTSD. There is little evidence in the literature for this practice. **Method:** Seventy-four patients from the Palo Alto Veterans Affairs Health Care System in California who were admitted to a specialized 8 week inpatient treatment program for PTSD were surveyed regarding their use of trazodone in the treatment of insomnia or nightmares. Patients were asked to complete a questionnaire regarding trazodone's effectiveness, side effects, and optimal doses. **Results:** Of 74 patients surveyed, 60 patients were able to maintain an effective dose of trazodone. The other 14 patients were unable to tolerate the medication. Seventy-two percent of the 60 patients assessed found trazodone helpful in decreasing nightmares, from an average of 3.3 to 1.3 nights per week ($p < .005$). Ninety-two percent found it helped with sleep onset, and 78% reported improvement with sleep maintenance. There was a significant correlation between the effectiveness in decreasing nightmares and improving sleep ($r = .57$, $p < .005$). The effective dose range of trazodone for 70% of patients was 50 to 200 mg nightly. Of the 74 patients surveyed, 9 (12%) reported priapism. **Conclusion:** Trazodone appears effective for the treatment of insomnia and nightmares associated with chronic PTSD. However, controlled trials are needed before any definite conclusions can be drawn. The higher than expected occurrence of priapism warrants clinicians asking directly about this side effect.

Introduction

It has become a common and accepted practice to treat insomnia with trazodone. Trazodone, a triazolopyridine derivative, was first marketed in the United States as an antidepressant in 1982. Some initial reports questioned its antidepressant efficacy but several subsequent reviews have substantiated it [2,7,8,30]. These initial reports questioning its efficacy may have contributed to the practice of trazodone as a sedative/hypnotic agent. A retrospective review of 30,000 patients found that one third of patients on a serotonin-selective reuptake inhibitor or clomipramine were using a secondary medication for insomnia and/or anxiety. The use of trazodone as the secondary agent was noted in 7.7% of patients [29].

Patients with post-traumatic stress disorder (PTSD) often have sleep disturbance [19]. Insomnia is part of the hyperarousal complex of symptoms and nightmares are characteristic in the symptom cluster of reliving the traumatic event. *Neylan* and associates performed an archival analysis on complaints about sleep based on data from the National Vietnam Veterans Readjustment study [24]. Three groups were compared as to sleep onset and maintenance insomnia and nightmares. The groups consisted of 1200 male Vietnam-theater veterans, 412 male Vietnam era veterans and 450 male civilian controls. Frequent nightmares were found exclusively in patients currently diagnosed with PTSD.

Patients with chronic PTSD are at high risk for substance abuse [3,4,14,18]. *Chilcoat* and *Breslan* [4] further noted that traumatic events alone without the diagnoses of PTSD, did not place patients at higher risk. The greatest risk of drug abuse/dependence was with prescribed psychoactive medications and not illegal drugs. They concluded that treatment of PTSD symptoms with psychoactive drugs may inadvertly contribute to drug abuse/dependence. Because trazodone is not an addictive medication, it may be particularly useful in a PTSD population to target insomnia and nightmares.

Method

There were 184 patients admitted from March to November 1998 to a specialized 8 week inpatient unit for the treatment of chronic PTSD at the Veterans Affairs Palo Alto Health Care System in California. Eighty patients were randomly assigned to one (CAP) of two psychiatrists and 74 met criteria for participation. All patients were male and (a) received a physical exam, (b) signed a written informed consent after study procedures were explained, (c) had a current DSM-IV diagnoses of PTSD that was confirmed on clinical exam by the admitting psychiatrist (CAP) and 68 patients had a Structured Clinical Interview of the DSM-IV (SCID). All patients who entered the study denied the use of alcohol or illicit drugs for a minimum of 30 days.

Patients were asked to participate if they had ever taken trazodone for insomnia or nightmares. Each survey was administered by a psychiatrist, psychologist or pharmacist. Fourteen of the 74 patients had intolerable side effects and

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discontinued the medication. Four the 60 patients continuing trazodone, orthostatic blood pressure and pulse were obtained.

The authors empirically designed a questionnaire addressing trazodone's efficacy in decreasing insomnia and the frequency or intensity of nightmares, optimal dosage, concurrent medications, and side effects. Data analysis was performed using the program SYSTAT 7.0 for those 60 patients maintained on trazodone. Improvement of insomnia and nightmares was rated on a 0 to 4 point scale and average improvement was assessed. A paired t-test was performed to assess the frequency of nightmares before and after trazodone use. Pearson correlations were performed on the 3 variables of optimal trazodone dose, helpfulness with decreasing nightmares, and improving sleep.

Results

All subjects were male and ranged in age from 28 to 60 years with a mean age of 50. All patients had a current diagnosis of chronic PTSD, as well as at least one comorbid diagnosis. Sixty-eight (92%) had major depressive disorder (MDD), and 55 (74%) had both MDD and a history of substance abuse (SA). Other comorbid diagnoses included anxiety disorders (7%) and bipolar disorder (4%).

Of 74 subjects who entered the study, 14 (19%) discontinued trazodone due to side effects either in the past or during their trial with trazodone in the program. Since only 60 subjects were able to reach an optimal dose, the following analysis was done with these subjects. All 60 stated trazodone was taken for insomnia and 55 stated it was also taken for nightmares (NM). The optimal dose for insomnia as well as nightmares ranged from 25 mg to 600 mg with 42 subjects (70%) on doses from 50 to 200 mg. The mean dose was 212 mg daily. The data was inspected to verify that assumptions for parametric analysis were met. Pearson correlations were performed with 3 variables: dose, helpfulness with nightmare (NM help) rating, and helpfulness with sleep (SLP help) rating. The NM help and SLP help correlation was .57 with $p < .005$, $n = 55$. There were no significant correlations between dose and either NM help ($r = -0.01$, $n = 55$) or SLP help ($r = .16$, $n = 60$). A paired t-test was performed with frequency (nights per week) of nightmares before (NMbe) and after (NMaf) trazodone use. The mean NMbe was 3.3 (SD = 1.7), the mean NMaf was 1.3 (SD = 1.4) with $t = 9.7$, $df = 54$ and $p < .005$.

Subjects rated trazodone's effectiveness for both overall sleep and nightmares as 0 – not helpful, 1 – minimally helpful, 2 – moderately helpful, 3 – extremely helpful. The values for sleep were: 7 subjects – 1, 29 subjects – 2, 24 subjects – 3 for a total of 60. The values for nightmares were 5 subjects – 0, 10 subjects – 1, 21 subjects – 2 and 19 subjects 3 for a total of 55. While 100% reported that trazodone helped with overall sleep, 55/60 subjects (92%) reported help with falling asleep and 47/60 subjects (78%) reported help with staying asleep. Forty of the 55 patients (73%) who used trazodone for nightmares reported moderate to significant decrease in nightmares.

Orthostatic blood pressures were taken on the 60 subjects, sitting for a minimum of 5 minutes and standing for one minute. Four subjects had a systolic drop of at least 20 mmHg but only one of these patients had symptoms. Six other subjects reported symptoms consistent with orthostasis but none had orthostatic changes. No subject discontinued trazodone secondary to orthostasis.

Concurrent medication use was evaluated for the 60 patients who reached an optimal trazodone dose. Ninety-eight percent (59 patients) were on another psychotropic medication. Fifty-eight patients (97%) used an antidepressant: 22 on nefazodone, 19 on paroxetine, 12 on sertraline and 5 on fluoxetine. Seventeen of the 60 patients (28%) also were using valproic acid. Eight patients (13%) used a benzodiazepine (lorazepam, alprazolam, diazepam, clonazepam). Six patients (10%) used an antipsychotic medication: 5 on olanzapine and 1 on risperidone. Miscellaneous medication use included one patient on diphenhydramine and one on oxycodone and hydrocodone. Only one of the 60 patients analyzed used trazodone as their sole psychotropic medication.

Of the 74 subjects, side effects which led to trazodone discontinuation in 14 subjects were: priapism (5 subjects), daytime sedation (5 subjects), more vivid nightmares (1 subject), severe dry mouth/dry sinus (1 subject), muscle pain (1 subject), and severe agitation (1 subject). Of the 60 patients who reached an optimal dose of trazodone while in the program, 36 reported side effects (60%); 26 reported daytime drowsiness, 14 reported dizziness, 6 reported headache, and 4 reported priapism. These 4 cases of priapism had all resolved, 3 with a decrease in dose and with the fourth case the initial dose was unknown. Thus in the initial group of 74 subjects 9 (12%) reported priapism, of which 5 discontinued the medication prior to the survey and 4 continued without further episodes.

Priapism was defined for patients as a painful or prolonged erection. Of the 9 patients with a report of priapism, concurrent medications were as follows. Four were only on trazodone, 2 did not know their concurrent medications, 2 were using sertraline (one with valproic acid), and one patient was on haloperidol, metoprolol and amlodipine. For the 8 patients whose dose at the time of the occurrence was known, the dose range was 50 to 450 mg daily, with an average of 190 mg daily. This average dose of 190 mg daily is slightly less than the average dose for all patients of 212 mg daily. For 3 of the 4 patients continuing with trazodone, the dose was decreased to a range of 25 to 100 mg daily. None of these 4 patients had further episodes. The average age of the 9 patients experiencing priapism was 47 years (range 25 – 53 years), which is similar to the average age of the entire group of 50 years old (range 28 – 60 years). Patients who had an episode of priapism described it as mild, moderate or severe in intensity and noted the duration of the episode. Of the 4 patients who continued trazodone after an episode of priapism, each rated the intensity as mild to moderate with less than an hour duration. Of those unwilling to retry trazodone after priapism, they rated the episode as moderate to severe intensity with a duration of greater than an hour. Only one patient who rated the intensity of the priapism as mild to moderate and less than an hour in duration did not want to retry trazodone, but not because of the episode but because he found excessive sedation with the medication intolerable.

Discussion

In the current survey, the use of trazodone to target sleep disturbance in patients with chronic PTSD appears to be effective. Trazodone was subjectively rated as moderately to significantly effective for decreasing nightmares in 72% of patients; 92% noted improvement in sleep onset insomnia and 78% reported improvement in sleep maintenance insomnia. There was a significant positive correlation between the usefulness of trazodone for nightmares and insomnia; and 92% of patients used it for both. Most patients (70%) were on doses between 50 to 200 mg daily.

Of the 74 patients in the survey, 19% discontinued the medication because of priapism (7%) or daytime sedation (7%). While daytime sedation is documented as a common side effect, the high rate of priapism was unexpected. Of the 74 patients, 9 (12%) reported at least one episode of priapism. The incidence of priapism with trazodone has been reported between 1 : 10000 to 1 : 1000 [11] and can occur in men who are impotent [16]. The exact mechanism whereby trazodone causes priapism is unknown, but it may be due to its alpha adrenergic blocking properties [15]. It is not clear why there is a higher than expected percentage of patients experiencing priapism in this current study. However, it may be due to direct questioning about this side effect or an additive effect with other psychotropic medications. Case reports have linked priapism to other psychotropic medications. Antidepressants including fluoxetine, sertraline, paroxetine, buproprion, and phenelzine, as well as, with antipsychotics such as olanzapine, risperidone, and fluphenazine hydrochloride are noted in the literature [1, 5, 6, 9, 17, 20, 23, 28, 31]. It seems possible that these medications may act synergistically with trazodone. However, 4 of the patients with priapism were solely on trazodone and of the 5 remaining on a concurrent medication, only 2 were on medications (sertraline, olanzapine) that have been anecdotally associated with priapism.

While 19% discontinued trazodone due to side effects, 60% of those continuing trazodone noted some side effect, predominately daytime sedation or dizziness. Trazodone has often been associated with orthostatic hypotension, which may account for the complaint of dizziness. All patients were monitored for orthostatic blood pressure changes. Six patients (10%) reported dizziness, but no orthostatic changes were noted. Four patients (7%) had documented orthostatic blood pressure changes but only one had associated symptoms. None of the patients discontinued the trial due to orthostatic blood pressure changes.

Six previous studies of depressed patients have reported trazodone effective for insomnia in 40 to 96% of patients. Four of these studies were open label, with sample sizes ranging from 5 to 48 patients [13, 22, 25, 32]. Patients were either on a monoamine oxidase inhibitor or fluoxetine. Trazodone in doses of 25 – 250 mg daily was added to target insomnia. One retrospective review of 13 depressed patients on a monoamine oxidase inhibitor medication demonstrated trazodone effective with 75% of patients with insomnia [26]. One double blind, placebo controlled, crossover study using trazodone in an average daily dose of 100 mg to treat insomnia in 15 depressed patients either on fluoxetine or buproprion found that 67% of patients had improved sleep with trazodone as compared to 13% with placebo [27]. The current finding of trazodone's effectiveness with insomnia in patients with PTSD is consistent with the previous studies with depressed patients with insomnia.

There have been 3 reports of the use of trazodone to treat PTSD. Two of these are single cases reports. *Menza* [21] noted a patient with PTSD was successfully treated with trazodone, at a dose of 300 mg daily. However the patient had to discontinue the medication due to a 2 hour episode of priapism. *Hargrave* [10] in a second case report noted the successful treatment of chronic PTSD in a patient with comorbid multi-infarct dementia. The patient, on 400 mg trazodone daily, had a decrease in nightmares and daytime flashbacks and night-time combativeness. The patient was also being treated with buspirone (15 mg TID) simultaneously.

Hertzberg et al. [12] studied six patients with combat-related PTSD and a comorbid history of major depression. The open label trial used an average dose of 300 mg daily of trazodone (range 50 to 400 mg). They reported that trazodone was effective in reducing symptoms of PTSD, beyond that of sleep disturbance symptoms. It is not clear whether they were also on concurrent psychotropic medications.

Summary

This current survey assesses trazodone's usefulness with sleep disturbance and nightmares in patients with PTSD. It is consistent with earlier suggestions that trazodone is effective to target insomnia and nightmares associated with PTSD. However, a limitation to any anecdotal data is the lack of a control group and the possible interaction with other medications. In this case, other medications could have enhanced or detracted from trazodone's efficacy. Patients with chronic PTSD noted significant subjective improvement of insomnia and nightmares with trazodone. An unexpected finding was the occurrence of priapism in 9 patients, 4 of whom were able to continue with treatment without further incidence. Priapism appears to be more common than previously reported. Double blind, placebo controlled trials of trazodone in the treatment of insomnia and nightmares in patients with PTSD are needed.

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References

[1] Ahmad S. Paroxetine-induced priapism. Arch Intern Med 1995; 155: 645
[2] Benkelfat C, Jay C, Renardet M. Use of interactive computer technology in open label clinical trials. Neuropsychobiology 1986; 15 (suppl 1): 48 – 56
[3] Brown PJ, Wolfe J. Substance abuse and post traumatic stress disorder comorbidity. Drug Alcohol Depend 1994; 35: 51 – 59
[4] Chilcoat HD, Breslan N. Post traumatic stress disorder and drug disorders. Arch Gen Psychiatry 1998; 55: 913 – 917

[5] Deirmenjian JM, Erhart SM, Wirshing DA, Spellberg BJ, Wirshing WC. Olanzapine-induced reversible priapism: a case report. J Clin Psychopharmacol 1998; 18 (4): 351 – 352
[6] Emes CE, Millson RC. Risperidone-induced priapism. Canadian Journal of Psychiatry 1994; 39 (4): 315 – 316
[7] Fabre LF. United States experience and perspectives with trazodone. Clin Neuropharmacol 1989; 12 (suppl): 511 – 517
[8] Feighner JP, Boyer WF. Overview of USA controlled trials of trazodone in clinical depression. Psychopharmacology 1988; 95: 550 – 553
[9] Fishbain DA. Priapism resulting from fluphenazine hydrochloride treatment reversed by diphenhydramine. Ann Emerg Med 1985; 14 (6): 600 – 602
[10] Hargrave R. Serotonergic agents in the management of dementia and post traumatic stress disorder. Psychosomatics 1993; 34: 461 – 462
[11] Haria M, Fitton A, McTavish D. Trazodone: A review of its pharmacology, therapeutic use in depression and therapeutic potential in other disorders. Drugs and Aging 1994; 4 (4): 331 – 355
[12] Hertzberg MA, Feldmann ME, Beckham JC, Davidson JRT. Trial of trazodone for post traumatic stress disorder using a multiple baseline group design. J Clin Psychopharmacol 1996; 16: 294 – 298
[13] Jacobsen FM. Low-dose trazodone as a hypnotic in patients treated with MAOIs and other psychotropics: a pilot study. J Clin Psychiatry 1990; 51: 298 – 302
[14] Kessler RC, Sonnega A, Bromet E, Hughes M, Nelson CB. Post traumatic stress disorder in the National Comorbidity Survey. Arch General Psychiatry 1995; 52: 1048 – 1060
[15] Kogeorgos J, de Alwis C. Priapism and psychtropic medication. Br J Psychiatry 1986; 149: 241 – 243
[16] Kulmala R, Lehtonen T, Nieminen P, Tammela T. Aetiology of priapism in 207 Patients. Eur Urol 1995; 28: 241 – 245
[17] Levenson JL. Priapism associated with buproprion treatment. Am J Psychiatry 1995; 152 (5): 813
[18] McFall ME, Mackay PW, Donovan DM. Combat-related post traumatic stress disorder and the severity of substance abuse in Vietnam veterans. J Stud Alcohol 1992; 53: 357 – 363
[19] Mellman TA, Kulick-Bell R, Ashlock LE, Nolan B. Sleep events among veterans with combat related post traumatic stress disorder. Am J Psychiatry 1995; 1: 110 – 115
[20] Mendelson WB, Franko T. Priapism with sertraline and lithium. J Clin Psychopharmacol 1994; 14 (6): 434 – 435
[21] Menza MA. Withdrawal syndrome in a depressed patient treated with trazodone. Am J Psychiatry 1986; 143: 1195
[22] Metz A, Shader RI. Adverse interactions encountered when using trazodone to treat insomnia associated with fluoxetine. Int Clin Psychopharmacol 1990; 5: 191 – 194
[23] Murray MJ, Hoobermann D. Fluoxetine and prolonged erection. Am J Psychiatry 1993; 150 (1): 167 – 168
[24] Neylan TC, Marmar CR, Metzler TJ, Weiss DS, Zatzick DF, Dehecchi KL, Wu RM, Schoenfeld FB. Sleep disturbances in the Vietnam generation: Findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry 1998; 155: 929 – 933
[25] Nierenberg AA, Cole JO, Glass L. Possible trazodone potentation of fluoxetine: a case series. J Clin Psychiatry 1992; 53: 83 – 85
[26] Nierenberg AA, Keck PE Jr. Management of monoamine oxidase inhibitor-associated insomnia with trazodone. J Clin Psychopharmacol 1989; 9: 42 – 45
[27] Nierenberg AA, Adler LA, Peselow E, Zornberg G, Rosenthal M. Trazodone for antidepressant-associated insomnia. Am J Psychiatry 1994; 151: 1069 – 1072
[28] Rand EH. Priapism in a patient taking sertraline. J Clin Psychiatry 1998; 59 (10): 538
[29] Rascertti K. Drug utilization review of concomittant use of specific serotonin reuptake inhibitors or clomipramine with antianxiety/sleep medications. Clinical Therapeutics 1995; 17: 786 – 790
[30] Schatzberg A. Trazodone: a 5-year review of antidepressant efficacy. Psychopathology 1987; 20 (suppl 1): 48 – 56
[31] Yeragani VK, Gershon S. Priapism related to phenelzine therapy. NEJM 1987; 327: 117 – 118
[32] Zimmer B, Doly F, Benjamin L. More on combination antidepressant therapy. Arch Gen Psychiatry 1984; 41: 527 – 528

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