An Open-Label, 12-Week Clinical and Sleep EEG Study of Nefazodone in Chronic Combat-Related Posttraumatic Stress Disorder

J. Christian Gillin, M.D.; Alison Smith-Vaniz, M.D.; Bradley Schnierow, M.D.; Mark H. Rapaport, M.D.; John Kelsoe, M.D.; Eric Raimo, M.D.; Matthew R. Marler, Ph.D.; Lorraine M. Goyette; Murray B. Stein, M.D.; and Sidney Zisook, M.D.

Background: We examined the effects of nefazodone on polysomnographic sleep measures and subjective reports of sleep quality and nightmares, as well as other symptoms, in patients with chronic combat-related posttraumatic stress disorder (PTSD) during a 12-week, open-label clinical trial. To our knowledge, this is the first polysomnographic study of treatment in patients with PTSD.

Method: The subjects were 12 male veterans (mean age = 54 years) who met DSM-IV diagnostic criteria for PTSD (mean duration = 30 years). All but 1 patient also met DSM-IV criteria for major depressive disorder. Patients were evaluated weekly with clinical ratings in an open-label clinical trial. Polysomnographic recordings for 2 consecutive nights were obtained before treatment and at 2, 4, 8, and 12 weeks. The dose of nefazodone was adjusted according to individual clinical needs. Final mean daily dose was 441 mg.

Results: The patients reported significantly fewer nightmares and sleep problems during treatment. Nevertheless, contrary to studies in depressed patients, nefazodone did not significantly affect polysomnographic sleep measures compared with baseline. In addition, the patients showed significant improvement in the Clinical Global Impressions of PTSD symptoms (global score, hyperarousals and intrusions subscales), the Clinician-Administered PTSD Scale (global, hyperarousal, and intrusions subscales), the Hamilton Rating Scale for Depression (HAM-D), and the Beck Depression Inventory (BDI).

Conclusion: These patients with chronic, treatment-resistant, combat-related PTSD showed significant improvement of subjective symptoms of nightmares and sleep disturbance, as well as depression and PTSD symptoms, in this 12-week open-label clinical trial. Nevertheless, objective polysomnographic sleep measures did not change. Further studies, including double-blind, placebo-controlled trials, are needed to extend these findings and to understand the relationships between the physiology of sleep and symptoms of poor sleep and nightmares.

(J Clin Psychiatry 2001;62:789–796)

Received Aug. 22, 2000; accepted March 6, 2001. From the University of California, San Diego and VA San Diego Healthcare System, San Diego.

Supported by Bristol-Myers Squibb.

Presented as a poster at the Annual Meeting of the Association of Professional Sleep Societies, June 19–24, 1999, Orlando, Fla.

Financial disclosure: Dr. Gillin has been a consultant for Aventis, Bristol-Myers Squibb, Eli Lilly, Medicus Group, Merck & Co., and Wyeth-Ayerst; and has carried out clinical trials with Bristol-Myers Squibb, Eli Lilly, Merck & Co., and Sepracor, Inc. Dr. Rapaport has been a consultant for Eli Lilly, Forest Pharmaceuticals, Janssen Pharmaceutica, Pfizer, Pharmacia, and Sanofi-Synthelabo; has received grant/research support from Abbott Laboratories, Bristol-Myers Squibb, Robert Wood Johnson, Eli Lilly, Forest Pharmaceuticals, Glaxo Wellcome, Novartis, Pfizer, Pharmacia, and Sanofi-Synthelabo; and has received honraria/speaking/travel support from Abbott Laboratories, Eli Lilly, Forest Pharmaceuticals, Novartis, Pfizer, Pharmacia, Sanofi-Synthelabo, and Wyeth-Ayerst. Dr. Stein has received research support from Bristol-Myers Squibb, Eli Lilly, Forest, Hoffmann-La Roche, Novartis, Parke-Davis, Pfizer, SmithKline Beecham, and Solvay; has been a consultant for Forest, Hoffmann-La Roche, Janssen, SmithKline Beecham, and Solvay; and has received speaking honoraria from Bristol-Myers Squibb, Eli Lilly, Hoffmann-La Roche, Pfizer, Pharmacia & Upjohn, SmithKline Beecham, and Solvay. Dr. Zisook has received grant/research support from Bristol-Myers Squibb, SmithKline Beecham, GlaxoWellcome, Pfizer, Eli Lilly, and Novartis and is on the speaker/advisory boards of GlaxoWellcome and SmithKline Beecham.

Reprint requests to: J. Christian Gillin, M.D., Psychiatry Service (116A), VA San Diego Healthcare System, 3350 La Jolla Village Dr., San Diego, CA 92161 (e-mail: jgillin@ucsd.edu).

Posttraumatic stress disorder (PTSD) is a common, chronic, and treatment-resistant disorder.[1] The estimated lifetime prevalence of PTSD in the United States is 10.4% in women and 5% in men.[1] Defining symptoms include *reexperiencing* (nightmares, intrusive thoughts, flashbacks, images, and memories), *avoidance* of trauma-related situations and *emotional blunting* (loss of interest and motivation, psychological detachment, and flattened affect), and *hyperarousal* (insomnia, hypervigilance, irritability, poor concentration, startle reactions). Traumatic experiences commonly associated with PTSD include combat, life-threatening accidents or natural disasters, rapes or sexual abuse, serious physical attacks or threats of attack, childhood physical abuse or neglect, and witnessing death or murder.[1] PTSD is often disabling and may be associated with comorbid conditions, particularly depression and dysthymia, obsessive-compulsive disor-

der, agoraphobia, generalized anxiety disorder, and alcoholism or substance abuse.[2,3]

PTSD is the only formal DSM-IV diagnosis (309.81) that includes 2 sleep symptoms—"recurrent distressing dreams of the [traumatic] event" and "difficulty falling asleep or staying asleep." All night sleep electroencephalographic (EEG) studies frequently demonstrate objective sleep abnormalities,[4–8] including shallow and fragmented sleep patterns, increased arousals or poor sleep maintenance,[6,9,10] loss of stages 3 and 4 sleep, increased rapid eye movement (REM) density,[6,9,11] short REM latency (the elapsed time between sleep onset and REM sleep onset),[6,11,12] and increased electromyographic activity in limbs.[13–15] Some studies, however, reported few or no abnormalities.[16] While dreaming and "ordinary" nightmares have usually been associated with REM sleep rather than non-REM sleep, some evidence suggests that PTSD nightmares may arise out of both states of sleep.[17,18]

The treatment of PTSD varies with the constellation of symptoms and the needs of each patient. It may include pharmacotherapy, psychotherapy and counseling, adjunctive therapies for comorbid conditions, family therapy, and support groups. No specific pharmacotherapy has been established for PTSD, but selective serotonin reuptake inhibitors (SSRIs),[19–21] tricyclic antidepressants,[22,23] bupropion,[24] and monoamine oxidase inhibitors (MAOIs)[25,26] have been reported to be clinically effective in open-label and controlled studies.[19,26]

This study was undertaken to assess the effects of nefazodone on the clinical symptoms and polysomnographic sleep patterns in patients with combat-related PTSD. We chose nefazodone for 2 reasons. First, previous studies, including our own,[27] suggested that nefazodone significantly improved clinical symptomatology in patients with PTSD.[28–30] Secondly, previous studies, again including some of our own,[31] suggested that it was an effective antidepressant that ameliorated both subjective sleep complaints and objective polysomnographic disturbances in patients with depression.[29,32]

In the current study, our a priori hypothesis was that nefazodone would significantly improve subjective sleep complaints, reduce nightmares, and improve objective polysomnographic sleep measures during the course of treatment compared with baseline measures obtained during a drug-free period before treatment with nefazodone. This is the first study to our knowledge that examines polysomnographic measures during treatment of patients with PTSD with any medication.

METHOD

The subjects were 12 male combat veterans who were a subgroup from our previously reported clinical study.[27] All patients met formal DSM-IV diagnostic criteria for PTSD. Subjects were recruited by flyers and by word of mouth from the PTSD and prisoner-of-war programs at the Veterans Affairs San Diego Healthcare System. Patients were excluded if they had a substance abuse disorder in the past 6 months. All subjects had a full medical and psychiatric history, a physical examination, laboratory tests, Clinical Global Impressions Severity scale for PTSD (CGI-S), the Clinician-Administered PTSD Scale,[33] Hamilton Rating Scale for Depression (HAM-D),[34] Beck Depression Inventory (BDI),[35] and Pittsburgh Sleep Quality Index.[36] Subjects were also screened for 1 night in the sleep laboratory to exclude sleep apnea and periodic limb movements of sleep.

At initial evaluation, patients had been drug free for at least 2 weeks. All had been treated with various antidepressants or anxiolytics previously, but without significant, long-term benefits. After completing diagnostic and research evaluations, subjects entered a 12-week open-label trial with nefazodone. The dose was determined by the treating clinician, starting at 50–100 mg b.i.d., and adjusted at weekly outpatient visits, at which time patients returned the BDI, the Epworth Sleepiness Scale,[37] and a subjective sleep diary, for the past week. The sleep diary, which patients were instructed to fill out daily, included a question on the number of nightmares per night; patients did not record the number of dreams or the content of the dreams. Patients were rated on the CGI every other week, on the HAM-D at weeks 2, 4, 8, and 12, and on the Pittsburgh Sleep Quality Index at weeks 4, 8, and 12.

Subjects slept in the sleep laboratory for 2 consecutive nights at baseline and weeks 2, 4, 8, and 12. On the sleep laboratory nights, subjects reported to the sleep laboratory about 9:30–10:30 p.m. Electrodes were placed for recording C3 or C4 EEG, by bilateral extraocular electro-oculogram (EOG), submental electromyogram (EMG), and electrocardiogram (ECG). Subjects retired about 10:30–11:30 p.m. and were awakened about 6:30 a.m. if they had not already arisen. Sleep records were scored visually by well-trained, experienced sleep technicians (interrater reliability > 0.80), using the Rechtschaffen-Kales criteria.[38]

The analyses of the treatment effects were performed in 2 complementary ways:

1. Each time series was modeled by a polynomial trend (orthogonal linear, quadratic, and cubic terms depending on the number of repeated observations), for each subject independent of all other subjects. The coefficient for each power and its corresponding t statistic was computed for each subject. Then the distributions of the coefficients (and corresponding t statistics) were tested by the Student t test and the Wilcoxon rank sum test to determine whether the mean coefficients were different from 0. Quadratic or cubic trends were rarely significantly different from 0.

Table 1. Demographic and Clinical Characteristics of 12 Male Veterans With Posttraumatic Stress Disorder

Age, y	
Mean ± SD	54 ± 10
Range	45–76
Education, y	13.5 ± 2.0
Marital status, N	
Married	2
Divorced	7
Widowed	2
Single	1
Occupation, N	
Unemployed	9
Employed	1
Retired	2
Race, N	
White	10
Hispanic	1
Native American	1
Branch of service, N	
Army	7
Navy	2
Marines	3
Military service, N	
WWII	2
Vietnam	10
PTSD age at onset, y	
Mean ± SD	24.8 ± 9.0
Range	18–50
PTSD duration, y	
Mean ± SD	30.3 ± 10.0
Range	17–55
Current comorbid DSM-IV Axis I diagnoses, N	
Substance abuse/dependence	10[a]
Major depressive disorder	11
Obsessive-compulsive disorder	2
Current DSM-IV Axis II diagnoses, N	
Borderline personality disorder	5
Antisocial personality disorder	1
Global Assessment of Functioning, initial score	
Mean ± SD	52.6 ± 6.0
Range	40–65

[a]All in full remission.

Table 2. Summary of Nefazodone Dosing Schedules (mg/day)

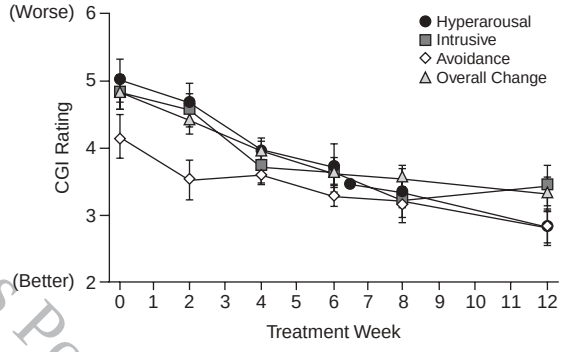
Dose	Week 2	Week 4	Week 6	Week 8	Week 12
Mean ± SD	254 ± 99	375 ± 136	475 ± 114	466 ± 107	441 ± 138
Minimum	50	200	300	300	200
Maximum	400	600	600	600	600

Table 3. Changes in Clinician-Administered PTSD Scale Scores in 12 Male Veterans

	Baseline		Week 12	
Subscale	Mean	SD	Mean	SD
Global	1.93	0.54	1.40	0.75*
Avoidance	1.44	0.80	1.48	1.00
Hyperarousal	2.10	0.53	1.54	0.81*
Intrusions	2.10	0.86	1.48	0.97*

*$p < .05$, paired t test.

Figure 1. The Effects of Nefazodone on Clinical Global Impressions: Severity of PTSD in 12 Male Veterans[a]



[a]Linear trends were statistically significant ($p < .01$) for hyperarousal, intrusive, and avoidance subscales, as well as overall change (Wilcoxon $S < -31$; $t < -4.0$). Quadratic trends were statistically significant ($p < .05$) for hyperarousal, avoidance, and overall change (Wilcoxon $S > 20$; $t > 2.0$).

2. The statistical significance of the linear, quadratic, and cubic trends was tested by linear mixed model analysis (SAS PROC MIXED) with random trends and several different models for errors on individuals (AR[1], variance components).[39]

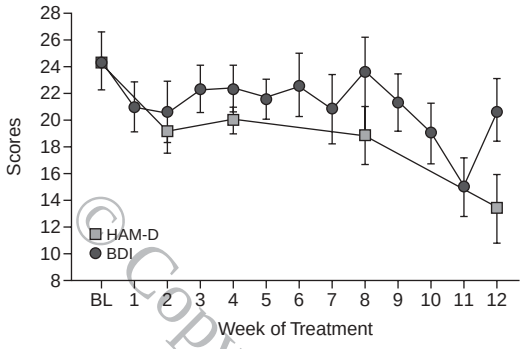
RESULTS

Fifteen patients were screened. Two were found to have sleep apnea and were excluded from the study. One patient entered but was diagnosed with lung cancer at the eighth week of the trial; he was discontinued and his data were excluded. The remaining 12 patients, who completed the study, suffered from chronic PTSD for a mean of 30 years starting at a mean age of about 25 years (Table 1). Ten were veterans of the Vietnam War, and 2 had been prisoners of war during World War II. Ten had previously met diagnostic criteria for substance abuse or dependence but were currently in full remission. Eleven currently met DSM-IV diagnostic criteria for major depressive disorder, but PTSD was the primary reason for seeking treatment. Depressive symptoms before treatment were significant, with mean levels on both the HAM-D and BDI of about 24. Their general level of functioning was poor, with an average initial Global Assessment of Functioning (GAF) score of 53.

The mean daily dose of nefazodone was increased from 254 mg/day at the end of the first week to a peak of 475 mg/day during week 6, and decreased slightly to a final mean dose of 441 mg/day in week 12 (Table 2).

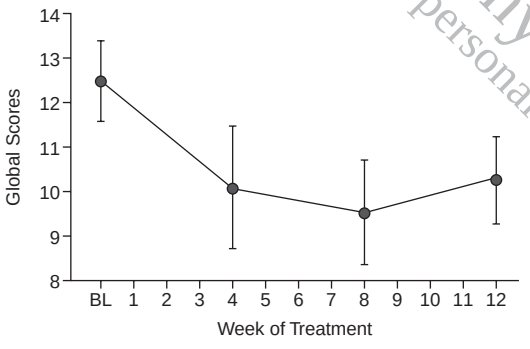
As expected from our larger clinical cohort of PTSD patients,[27] the patients showed statistically significant improvement on the Clinician-Administered PTSD Scale (global scale, hyperarousal and intrusions subscales, but not the avoidance subscale) (Table 3), the Clinical Global Impressions Severity of PTSD (Figure 1), the HAM-D, and the BDI (Figure 2) over the 12-week trial.

Figure 2. The Effects of Nefazodone on Mood as Measured by the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI)[a]



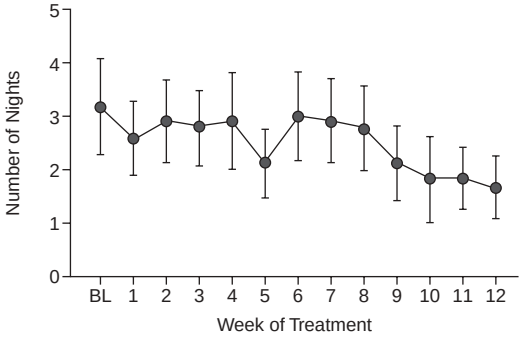
[a]The improvement on both scales was statistically significant by both Wilcoxon and mixed models for linear trends:
HAM-D: Wilcoxon S = –31, p = .01; mixed model t = –3.2, df = 46, p = .003.
BDI: Wilcoxon S = –25, p = .05; mixed model t = –2.20, df = 128, p = .03.
Abbreviation: BL = baseline.

Figure 3. The Effects of Nefazodone on the Pittsburgh Sleep Quality Index[a]



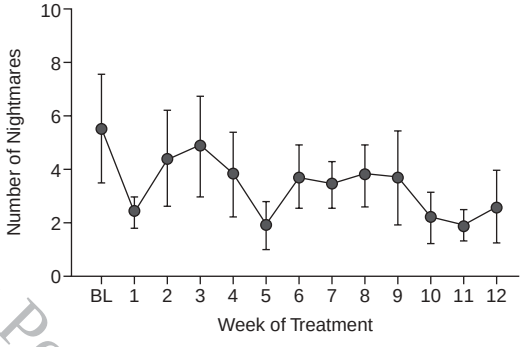
[a]The improvement of reported sleep quality was statistically significant by both Wilcoxon and mixed models for linear trends, but not for quadratic trends:
Linear trend: Wilcoxon S = –37.5, p = .006; mixed model: t = –3.6, df = 32, p = .001.
Quadratic trend: Wilcoxon S = 22, p = .09; mixed model t = 1.77, df = 32, p = .09.

Figure 4. Nights With Nightmares in the Past Week[a]



[a]Number of nights with nightmares improved significantly by both Wilcoxon and mixed models for linear trends: Wilcoxon S = –25, p = .02; mixed model t = –2.19, df = 108, p = .03.

Figure 5. The Number of Nightmares in the Past Week[a]



[a]Number of nightmares per week improved significantly by both Wilcoxon and mixed models for linear trends: Wilcoxon S = –25, p = .02; mixed model t = –2.14, df = 106, p = .03.

Consistent with our hypothesis, the patients reported significant improvement in their subjective sleep quality as measured by the Pittsburgh Sleep Quality Index (Figure 3). In addition, patients reported fewer nightmares on their weekly sleep questionnaires; nights with nightmares were reduced by an average of about 1 less night per week (Figure 4). Total nightmares were reduced by almost 2 less nightmares per week (Figure 5).

Despite the subjective improvements in sleep quality and nightmares, polysomnographic measures did not change significantly during the trial compared with baseline values (Table 4). While no control group was studied, the objective sleep measures in these PTSD patients were characterized by reduced total sleep time, sleep efficiency, delta sleep, and REM latency in comparison to published norms[40] for age-matched men.

DISCUSSION

Of particular interest in this study, subjective sleep quality increased and number of reported nightmares decreased in the absence of significant changes in polysomnographic sleep measures. At the end of the 12-week trial compared with baseline, the mean global score on the Pittsburgh Sleep Quality Index dropped by about 20%, while the mean number of reported nightmares per week dropped by about 30%. The only change in objective sleep measures that approached statistical significance was increased delta (stages 3 and 4) sleep percentage in weeks 8 and 12; otherwise, the sleep measures, including REM sleep, changed very little compared with baseline. The declines in poor sleep quality and nightmares are important findings in their own right; these symptoms are

Table 4. Polysomnographic Summaries for 12 Male Veterans[a]

Measure	Baseline	Week 2	Week 4	Week 8	Week 12
Sleep latency	15 ± 3	16 ± 3	15 ± 3	25 ± 6	21 ± 4
Total sleep time	358 ± 10	359 ± 13	363 ± 13	362 ± 21	372 ± 17
Sleep efficiency, %	85.5 ± 1.6	85.5 ± 2.0	83.0 ± 2.0	82.0 ± 3.0	84.3 ± 2.5
Awake in bed	38 ± 7	39 ± 10	53 ± 13	43 ± 11	40 ± 9
Delta, %	4.0 ± 1.4	2.8 ± 1.4	2.5 ± 0.9	9.0 ± 4.0	16.8 ± 4.1
Rapid eye movement, %	26.2 ± 2.0	23.4 ± 1.8	24.6 ± 2.0	26.1 ± 2.1	26.3 ± 2.6
REM density	2.3 ± 0.2	2.3 ± 0.3	2.7 ± 0.3	2.3 ± 0.3	2.6 ± 0.4
REM latency	54 ± 6	48 ± 5	63 ± 6	54 ± 6	58 ± 8

[a]Values are in minutes (mean ± SD) except for SE%, delta%, REM%, and REM density (0–8/min).

vexing and treatment resistant in patients with combat-related PTSD, but these data are all the more interesting since these patients did not exhibit improved objective sleep changes. Aside from the clinical implications, these observations raise important questions about the psychophysiologic mechanisms underlying nightmares, poor sleep quality, and their treatment.

When we planned this study, we expected that objective sleep measures would improve significantly during treatment with nefazodone. This expectation was based on several studies in which nefazodone significantly improved objective sleep measures in patients with depression.[41–43] In previous studies in depressed patients, nefazodone significantly improved both subjective sleep quality and objective sleep efficiency and wake time after sleep onset compared with either before-treatment values or values in a randomized, parallel group of depressed patients treated with fluoxetine.[42,44] The lack of objective sleep change in the current study may be testimony to the symptomatic severity and chronicity of this group of severely impaired combat veterans. No other published studies exist, to our knowledge, on the effects of pharmacologic therapy on polysomnography in patients with PTSD. Further studies are needed to determine the effects of antidepressants or other medications on sleep EEG of PTSD patients. In addition, further studies are needed to test the hypothesis that antidepressants affect polysomnographic sleep measures in depressed patients but not PTSD patients.

Several studies claimed that nefazodone improved subjective sleep quality, nightmare symptoms, or intrusive symptoms in PTSD patients.[29,45–47] In a study of combat-related PTSD patients, Mellman et al.[48] recently reported that nefazodone reduced reports of traumatic events during dreaming at 6 weeks of treatment compared with baseline. Consistent with the strong relationships between nightmares and PTSD, Neylan et al.[49] found that frequent nightmares occurred almost exclusively in Vietnam veterans with current PTSD.

In addition to the practical, clinical management of traumatic nightmares, the role of REM sleep in their pathophysiology is of considerable theoretical importance. More than a decade ago, Ross et al.[50] hypothesized that PTSD might be a pathophysiologic disorder of REM sleep. His hypothesis was based in part on the fact that recurrent dreams and flashbacks were characteristic symptoms of PTSD.

Although dreams and nightmares were traditionally thought to arise almost exclusively from REM sleep, increasing evidence indicates that they may occur in non-REM sleep in addition to REM sleep.[17,51,52] Van der Kolk et al.[18] and others have suggested that PTSD nightmares may arise out of both states of sleep.

Subjective changes in sleep quality, dreaming, and nightmares may be independent of objective changes in REM sleep, delta sleep, sleep efficiency, total sleep time, or other conventional sleep EEG measures in depressed or PTSD patients. In our 8-week clinical trial in 125 depressed patients, subjective sleep quality and ratings of depression improved in both the nefazodone and fluoxetine groups; nevertheless, objective sleep efficiency increased and number of awakenings decreased significantly in the nefazodone group; the opposite occurred in the fluoxetine group.[42] Furthermore, compared with baseline measures before treatment, REM sleep was unaffected in the nefazodone group and suppressed in the fluoxetine group. It appeared that improvement in the subjective sleep measures was better accounted for by the improvement in depressive ratings than changes in polysomnographic measures.

The interpretation of the relationship between polysomnographic recordings and dream or nightmare reports is further complicated by observations in a recent study with a drug that completely eliminates REM sleep. Phenelzine, a monoamine oxidase inhibitor, was administered in 11 depressed patients for 5 weeks in an open-label trial.[53] REM sleep was virtually absent in both responders and nonresponders by the fifth week of treatment. Before treatment, the 6 patients who were eventually rated as responders at 5 weeks reported more dreams per week than the 5 patients who would be nonresponders; the frequency of dreams each week declined dramatically in the responders but increased in the nonresponder group during the 5-week trial.

It remains to be seen, however, whether drugs, such as phenelzine or other monoamine oxidase inhibitors that eliminate REM sleep in depressed patients, would provide better relief of nightmares or sleep complaints than other antidepressants that do not affect REM sleep (like nefazodone) or do not suppress it completely (like sertraline and other SSRIs). Previous case reports and studies have specifically reported that phenelzine decreased nightmares[25,54–58] or improved sleep in PTSD patients. The effect of MAOIs on polysomnographic sleep in PTSD patients has not been studied to our knowledge.

At the present time, sertraline (an SSRI) is the only drug approved by the U.S. Food and Drug Administration for treatment of PTSD. It suppresses REM sleep more than nefazodone and less than phenelzine. In a large double-blind clinical study in mostly civilian patients with PTSD, subjective insomnia was rated greater in the sertraline group than the placebo group, even though the sertraline group showed significantly greater reduction of PTSD symptoms than the placebo group.[21]

Consistent with the reciprocal cholinergic-aminergic hypothesis for the regulation of REM sleep, we can say with some confidence that cholinergic, muscarinic induction of REM sleep is associated with dreaming.[59] We previously demonstrated that dreaming was associated with REM sleep induced by intravenous administration of physostigmine, a cholinesterase inhibitor, during non-REM sleep in normal volunteers.[60] With placebo infusions, dreaming was reported when subjects were awakened during non-REM sleep but at a lower rate than awakenings during REM sleep. The normal rate of dreaming during non-REM sleep was not affected by administration of physostigmine compared with placebo.

The other side of the reciprocal interaction hypothesis is that REM sleep is suppressed by serotonergic and noradrenergic neurotransmission. Phenelzine suppression of REM sleep appears to be dependent upon serotonergic neurotransmission, that is, REM sleep is restored when the REM-suppressed patients are administered the tryptophan-free drink, which depletes the brain of serotonin.[61] Several other medications—prazosin (an α_1-adrenergic antagonist),[62] cyproheptadine (an antihistamine),[42,63–65] and guanfacine (a central α_2-adrenergic stimulant)[66]—apparently reduce the rate of nightmares, although the mechanisms vary and are poorly understood. On the other hand, nightmares have been associated with administration of sedatives, β-blockers, amphetamines, and dopamine agonists.[67,68]

While the medication was well tolerated by those patients who completed the study, 1 patient, a 51-year-old man with a history of PTSD, depression, alcoholism in remission, and nephrectomy 5 years previously, experienced hypersomnia (reported sleeping 14–18 hours per day) while being treated with nefazodone (400 mg/day) during the eighth week of treatment. On all night polysomnography, he showed no evidence of sleep-related breathing disorders either before or during treatment with nefazodone. His daily dose was reduced to 200 mg/day, and he continued the trial without difficulty. Some of the other patients did report increased sedation during the daytime from time to time, especially the older men, but they improved with lowered doses. In the entire group of patients who completed the trial, nefazodone had no effect on the Epworth scale, a subjective measure of weekly daytime sleepiness.

As mentioned earlier, the patients in this sleep study were a subgroup from our larger open-label clinical trial with nefazodone.[27] Chronic combat-related PTSD improved significantly compared with baseline as measured by symptoms of PTSD (Clinician-Administered PTSD Scale, Clinical Global Impressions of Severity of PTSD) and depression ratings (HAM-D, BDI), in addition to subjective sleep quality (Pittsburgh Sleep Quality Index) and nightmares. The general mean rates of improvement for the whole group were in the range of 20% to 50% reduction in clinical symptoms. Although none of these patients achieved a symptom-free state during treatment, the benefits were clinically significant, perhaps even impressive, given the chronicity, severity, and treatment resistance of this group of patients. Since this was an open-label study, the present results warrant future well-controlled studies in which the effects of nefazodone would be compared with placebo or other medications.

While the overall results of this open trial of nefazodone are promising, the nature of this study may limit generalizations to other types of PTSD. First, all of our subjects were middle-aged or elderly male subjects who suffered from chronic combat-related PTSD. Secondly, as commonly found in veterans with combat-related PTSD, nearly all of our subjects presently had or had previously had significant comorbid diagnoses, including major depression or substance/alcohol abuse. For these reasons, the clinical response to nefazodone or other medications might differ in women compared to men with PTSD, in patients with acute or semi-acute rather than chronic PTSD, or in patients without, compared to those with, comorbid diagnoses. Furthermore, the polysomnographic sleep characteristics of our patients are not easy to interpret because of the age, chronicity of the PTSD syndrome, and the presence of comorbid diagnoses that also affect sleep.

In summary, these results suggest that nefazodone significantly ameliorates PTSD symptoms, mood, subjective sleep quality, and the rate of nightmares in treatment-resistant patients with chronic combat-related PTSD in the absence of significant changes in objective EEG sleep measures. Further, well-controlled studies are needed to evaluate this hypothesis, as well as to determine whether symptoms continue to improve with ongoing treatment beyond 12 weeks.

Drug names: bupropion (Wellbutrin and others), cyproheptadine (Periactin), fluoxetine (Prozac), guanfacine (Tenex and others), nefazodone (Serzone), phenelzine (Nardil), prazosin (Minipress and others), sertraline (Zoloft).

REFERENCES

1. Kessler RC, Sonnega A, Bromet E, et al. Posttraumatic stress disorder in the national comorbidity survey. Arch Gen Psychiatry 1995;52:1048–1060
2. Keane TM, Kaloupek DG. Comorbid psychiatric disorders in PTSD: implications for research. In: Yehuda R, McFarlane AC, eds. Annals of the New York Academy of Sciences, vol 821. New York, NY: The New York Academy of Sciences; 1997:24–34
3. Breslau N, Davis GC, Andreski P, et al. Traumatic events and posttraumatic stress disorder in an urban population of young adults. Arch Gen

Psychiatry 1991;48:216–222
4. Mellman TA. Psychobiology of sleep disturbances in posttraumatic stress disorder. In: Yehuda R, McFarlane AC, eds. Annals of the New York Academy of Sciences, vol 821. New York, NY: The New York Academy of Sciences; 1997:142–149
5. Mellman TA, Kulick-Bell R, Ashlock LE, et al. Sleep events among veterans with combat-related posttraumatic stress disorder. Am J Psychiatry 1995;152:110–115
6. Dow BM, Kelsoe JRJ, Gillin JC. Sleep and dreams in Vietnam PTSD and depression. Biol Psychiatry 1996;39:42–50
7. Lavie P, Hefez A, Halperin G, et al. Long-term effects of traumatic war-related events on sleep. Am J Psychiatry 1979;136:175–178
8. Woodward SH, Friedman MJ, Bliwise DL. Sleep and depression in combat-related PTSD inpatients. Biol Psychiatry 1996;39:182–192
9. Mellman TA, Nolan B, Hebding J, et al. A polysomnographic comparison of veterans with combat-related PTSD, depressed men, and non-ill controls. Sleep 1997;20:46–51
10. Woodward SH, Bliwise DL, Friedman MJ, et al. Subjective versus objective sleep in Vietnam combat veterans hospitalized for PTSD. J Trauma Stress 1996;9:137–143
11. Ross RJ, Ball WA, Dinges DF, et al. Rapid eye movement sleep disturbance in posttraumatic stress disorder. Biol Psychiatry 1994;35:195–202
12. Reist C, Kauffman CD, Chicz-DeMet A, et al. REM latency, dexamethasone suppression test, and thyroid releasing hormone stimulation test in posttraumatic stress disorder. Prog Neuropsychopharmacol Biol Psychiatry 1995;19:433–443
13. Ross RJ, Ball WA, Dinges DF, et al. Motor dysfunction during sleep in posttraumatic stress disorder. Sleep 1994;17:723–732
14. Lavie P, Hertz G. Increased sleep motility and respiration rates in combat neurotic patients. Biol Psychiatry 1979;14:983–987
15. Brown TM, Boudewyns PA. Periodic limb movements of sleep in combat veterans with posttraumatic stress disorder. J Trauma Stress 1996;9: 129–136
16. Hurwitz TD, Mahowald MW, Kuskowski M, et al. Polysomnographic sleep is not clinically impaired in Vietnam combat veterans with chronic posttraumatic stress disorder. Biol Psychiatry 1998;44:1066–1073
17. Hartmann E. Dreams and Nightmares: The New Theory on the Origin and Meaning of Dreams. Cambridge, Mass: Perseus Books; 1998
18. van der Kolk B, Blitz R, Burr W, et al. Nightmares and trauma: a comparison of nightmares after combat with lifelong nightmares in veterans. Am J Psychiatry 1984;141:187–190
19. Davidson JRT. Biological therapies for posttraumatic stress disorder: an overview. J Clin Psychiatry 1997;58(suppl 9):29–32
20. Dow B, Kline N. Antidepressant treatment of posttraumatic stress disorder and major depression in veterans. Ann Clin Psychiatry 1997;9:1–5
21. Brady KT, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000;283:1837–1844
22. Kosten TR, Frank JB, Dan E, et al. Pharmacotherapy for posttraumatic stress disorder using phenelzine or imipramine. J Nerv Ment Dis 1991; 179:366–370
23. Frank JB, Kosten TR, Giller EJ, et al. A randomized clinical trial of phenelzine and imipramine for posttraumatic stress disorder. Am J Psychiatry 1988;145:1289–1291
24. Cañive JM, Clark RD, Calais LA, et al. Bupropion treatment in veterans with posttraumatic stress disorder: an open study. J Clin Psychopharmacol 1998;18:379–383
25. Lerer B, Bleich A, Kotler M, et al. Posttraumatic stress disorder in Israeli combat veterans: effect of phenelzine treatment. Arch Gen Psychiatry 1987;44:976–981
26. Katz RJ, Lott MH, Arbus P, et al. Pharmacotherapy of post-traumatic stress disorder with a novel psychotropic. Anxiety 1994;1:169–174
27. Zisook S, Chentsova-Dutton YE, Smith-Vaniz A, et al. Nefazodone in patients with treatment refractory posttraumatic stress disorder. J Clin Psychiatry 2000;61:203–208
28. Hertzberg MA, Feldman ME, Beckman JC, et al. Open trial of nefazodone for combat-related posttraumatic stress disorder. J Clin Psychiatry 1998; 59:460–464
29. Hidalgo R, Hertzberg MA, Mellman T, et al. Nefazodone in post-traumatic stress disorder: results from six open-label trials. Int Clin Psychopharmacol 1999;14:61–68
30. Davidson JRT, Weisler RH, Malik ML, et al. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol 1998;13: 111–113
31. Gillin JC, Rapaport M, Erman MK, et al. A comparison of nefazodone and fluoxetine on mood and on objective, subjective, and clinician-rated measures of sleep in depressed patients: a double-blind, 8-week clinical trial. J Clin Psychiatry 1997;58:185–192. Correction 1997;58:275
32. Sharpley AL, Williamson DJ, Attenburrow MEJ, et al. The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. Psychopharmacology (Berl) 1996;126:50–54
33. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale. J Trauma Stress 1995;8:75–90
34. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
35. Beck AT, Ward C, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1963;4:561–571
36. Buysse DJ, Reynolds CF III, Monk TH, et al. The Pittsburgh Sleep Quality Index: a new instrument for psychiatric practice and research. Psychiatry Res 1989;28:193–213
37. Johns MW. Daytime sleepiness, snoring, and obstructive sleep apnea: The Epworth Sleepiness Scale. Chest 1993;103:30–36
38. Rechtschaffen A, Kales A. A manual of standard techniques and scoring system for sleep stages in human subjects. Washington, DC: US Government Printing Office; 1971
39. Marler M, Jacob RG, Lehoczky J, et al. The statistical analysis of treatment effects in 24-hour ambulatory blood pressure recordings. Stat Med 1987;7:259–270
40. Gillin JC, Duncan W, Pettigrew KD, et al. Successful separation of depressed, normal, and insomnia patients by EEG sleep data. Arch Gen Psychiatry 1979;36:85–90
41. Armitage R, Rush AJ, Trivedi M, et al. The effects of nefazodone on sleep architecture in depression. Neuropsychopharmacology 1994;10:123–127
42. Rush AJ, Armitage R, Gillin JC, et al. Comparative effects of nefazodone and fluoxetine on sleep in outpatients with major depressive disorder. Biol Psychiatry 1998;44:3–14
43. Sharpley AL, Williamson DJ, Attenburrow ME, et al. The effects of paroxetine and nefazodone on sleep: a placebo controlled trial. Psychopharmacology (Berl) 1996;126:50–54
44. Armitage R, Yonkers K, Cole D, et al. A multicenter, double-blind comparison of the effects of nefazodone and fluoxetine on sleep architecture and quality of sleep in depressed outpatients. J Clin Psychopharmacol 1997;17:161–168
45. Davidson JRT, Weissler RH, Malik ML, et al. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol 1998;13: 111–113
46. Davis LL, Nugent AL, Murray J, et al. Nefazodone treatment for chronic posttraumatic stress disorder: an open trial. J Clin Psychopharmacol 2000; 20:159–164
47. Clark RD, Canive JM, Calais LA, et al. Nefazodone in post traumatic stress disorder: a retrospective chart review. Psychline 1998; 21–28
48. Mellman TA, David D, Barza L. Nefazodone treatment and dream reports in chronic PTSD. Depress Anxiety 1999;9:146–148
49. Neylan TC, Marmar CR, Metzler TJ, et al. Sleep disturbances in the Vietnam generation: findings from a nationally representative sample of male Vietnam veterans. Am J Psychiatry 1998;155:929–933
50. Ross RJ, Ball WA, Sullivan KA, et al. Sleep disturbance as the hallmark of posttraumatic stress disorder. Am J Psychiatry 1989;146:697–707
51. Kramer M, Kinney L. Sleep patterns in trauma victims with disturbed dreaming. Psychiatr J University Ottawa 1988;13:12–16
52. Hartmann E. The Nightmare: The Psychology and Biology of Terrifying Dreams. New York, NY: Basic Books; 1984
53. Landolt HP, Raimo EB, Schnierow BJ, et al. Sleep and sleep electroencephalogram in depressed patients treated with phenelzine. Arch Gen Psychiatry 2001;58:268–276
54. Hogben GL, Cornfield RB. Treatment of traumatic war neurosis with phenelzine. Arch Gen Psychiatry 1981;38:440–445
55. Walker JI. Chemotherapy of traumatic war stress. Milit Med 1982;147: 1029–1033
56. Levenson H, Lanman R, Rankin M. Traumatic war neurosis and phenelzine [letter]. Arch Gen Psychiatry 1982;39:1345
57. Davidson J, Walker JI, Kilts C. A pilot study of phenelzine in the treatment of post-traumatic stress disorder. Br J Psychiatry 1987;150:252–255
58. Trudeau DL, Anderson J, Hansen LM, et al. Findings of mild traumatic brain injury in combat veterans with PTSD and a history of blast concussion. J Neuropsychiatry Clin Neurosci 1998;10:308–313

59. Hobson JA. The Dreaming Brain. New York, NY: Basic Books; 1988
60. Sitaram N, Moore AM, Gillin JC. The effect of physostigmine on normal sleep and dreaming. Arch Gen Psychiatry 1978;35:1239–1245
61. Landolt HP, Schnierow BJ, Kelsoe JR, et al. Phenelzine-induced suppression of REM sleep can be reversed by rapid tryptophan depletion [abstract]. Sleep 2000;23(suppl 2):A34–A35
62. Raskind MA, Dobie DJ, Kanter ED, et al. α_1-Adrenergic antagonist prazosin ameliorates combat trauma nightmares in veterans with posttraumatic stress disorder: a report of 4 cases. J Clin Psychiatry 2000;61:129–133
63. Brophy MH. Cyproheptadine for combat nightmares in posttraumatic stress disorder and dream anxiety disorder. Milit Med 1991;156:100–101
64. Gupta S, Austin R, Cali LA, et al. Nightmares treated with cyproheptadine [letter]. J Am Acad Child Adolesc Psychiatry 1998;37:570–572
65. Harach HH. Cyproheptadine for recurrent nightmares. Am J Psychiatry 1986;143:1491–1492
66. Horrigan JP, Barnhill LJ. The suppression of nightmares with guanfacine [letter]. J Clin Psychiatry 1996;57:371
67. Thompson DF, Pierce DR. Drug-induced nightmares. Ann Pharmacother 1999;33:93–98
68. Yamada Y, Shibuya F, Hamada J, et al. Prediction of sleep disorders induced by beta-adrenergic receptor blocking agents based on receptor occupancy. J Pharmacokinet Biopharmaceutics 1995;23:131–145