The Effect of Nefazodone on Subjective and Objective Sleep Quality in Posttraumatic Stress Disorder

Thomas C. Neylan, M.D.; Maryanne Lenoci, M.A.; Melissa L. Maglione, B.A.; Nicholas Z. Rosenlicht, M.D.; Yan Leykin, B.A.; Thomas J. Metzler, M.A.; Frank B. Schoenfeld, M.D.; and Charles R. Marmar, M.D.

Background: This study assesses the efficacy of nefazodone treatment (target dose of 400–600 mg/day) on objective and subjective sleep quality in Vietnam combat veterans with chronic DSM-IV posttraumatic stress disorder (PTSD).

Method: Medically healthy male Vietnam theater combat veterans with DSM-IV PTSD (N = 10) completed a 12-week open-label trial. Two nights of ambulatory polysomnography were obtained at baseline and at the end of the trial. PTSD and depressive symptoms and subjective sleep quality were assessed at baseline and after 12 weeks. Data were collected in 1999 and 2000.

Results: Nefazodone treatment led to a significant decrease in PTSD and depressive symptoms ($p < .05$), an improvement in global subjective sleep quality, and a reduction in nightmares. Nefazodone also resulted in a substantial improvement in objective measures of sleep quality, particularly increased total sleep time, sleep maintenance, and delta sleep as measured by period amplitude analysis.

Conclusion: Nefazodone therapy results in an improvement of both subjective and objective sleep quality in subjects with combat-related PTSD.

(J Clin Psychiatry 2003;64:445–450)

Received Jan. 29, 2002; accepted Aug. 8, 2002. From the Department of Psychiatry, University of California, San Francisco, and the Psychiatry Service, San Francisco Veterans Affairs Medical Center.

Supported by grant MH057157 from the National Institutes of Health, Bethesda, Md. (Dr. Neylan); Bristol-Myers Squibb, Princeton, N.J. (Dr. Neylan); and the General Clinical Research Center, Moffitt Hospital, University of California, San Francisco, with funds provided by grant 5 M01 RR-00079 from the National Center for Research Resources, U.S. Public Health Service.

Corresponding author and reprints: Thomas C. Neylan, M.D., PTSD Program, Psychiatry Service 116P, VA Medical Center, 4150 Clement St., San Francisco, CA 94121 (e-mail: neylan@itsa.ucsf.edu).

Sleep disturbances are the most frequently reported complaints by veterans receiving treatment in Veterans Affairs specialty clinics for posttraumatic stress disorder (PTSD).[1] Woodward and colleagues[2] have published the only study that employed quantitative analysis of the sleep electroencephalogram (EEG) in this population. In their study, a distinguishing feature in a sample of 56 unmedicated Vietnam combat veterans was that subjects with PTSD compared with controls had significantly decreased delta sleep spectral power during non–rapid eye movement (NREM) sleep. Data from multiple studies support the hypothesis that delta sleep is primarily linked to sleep depth and the homeostatic and physical restorative function of sleep.[3–5]

Nefazodone is known to improve sleep continuity, an effect presumably related to its antagonism of serotonin type 2 (5-HT_2) receptors.[6] Several studies in depressed subjects have shown that nefazodone improves objective measures of sleep quality as measured by visual sleep staging.[7–9] Open trials of nefazodone in subjects with PTSD have shown that it reduces PTSD symptoms and improves subjective sleep quality,[10–13] though limited objective data are available. Mellman and colleagues[14] reported that nefazodone treatment resulted in improved subjective sleep quality and a reduction in trauma-related dream content. They found that objective sleep continuity, as measured by visual sleep staging, improved in 4 subjects for whom they had polysomnographic recordings at baseline and after treatment. Gillin and colleagues[15] reported that nefazodone improved PTSD and depressive symptoms and subjective sleep quality in 12 male subjects with combat-related PTSD, but did not result in significant improvements in visually scored polysomnographic sleep measures. To date, no study has examined the effect of nefazodone on quantitative measures of the sleep EEG.

Studies of several chemically distinct antagonists of 5-HT_2 receptors document that these agents increase levels of delta sleep (EEG power in 0.3–4.0 Hz band) in humans and animals (reviewed in Landolt et al.[16]). Studies of the effect of specific 5-HT_2 receptor antagonists, such as ritanserin and seganserin, on sleep show that these

agents produce increases in delta sleep.[16–20] Nefazodone is known to antagonize 5-HT_2 receptors,[6] but no study has carefully determined if it produces increases in quantitative delta sleep. Most polysomnographic studies of nefazodone have shown no effect on specific sleep stages,[7,21,22] though a small number of studies have shown modest increases in REM sleep.[23,24] Although no study has shown a significant impact of nefazodone on visually scored delta sleep, the study by Gillin and colleagues[15] showed that visually scored delta sleep percentage went from a mean ± SD of 4.0 ± 1.4% to 16.8 ± 4.1% at the end of the trial at week 12, a difference that approached statistical significance.

Visual scoring is based on arbitrary criteria that produce crude category scores for each epoch of sleep masking the complexity of the underlying EEG signal. Further, since delta sleep typically represents a small fraction of total sleep time, most clinical studies lack the power to detect significant changes with treatment. Period amplitude analysis (PAA) is a method of quantitative sleep EEG analysis that is particularly powerful for examining activity in slow frequency bands.[25] It is a time-domain technique that measures amplitude and counts EEG activity within predetermined bandwidths such as the slow-wave, or delta, frequencies.[25,26]

We report here the results of an open-label trial of nefazodone therapy in a sample of 10 male combat veterans with chronic PTSD. The specific focus is on the effect of nefazodone on different domains of sleep disturbances in subjects with chronic PTSD. We hypothesized that nefazodone treatment would be associated with improvements in sleep duration, global sleep quality, and a reduction in nightmares. Further, given that nefazodone antagonizes 5-HT_2 receptors, we hypothesized that this agent would result in an increase in quantitative delta sleep as measured by PAA.

METHOD

Subjects

Medically healthy male Vietnam theater combat veterans (N = 10) were recruited from the outpatient PTSD clinical program at the San Francisco Veterans Affairs Medical Center (San Francisco, Calif.). All subjects gave their informed consent after the procedures and possible adverse effects were fully explained. The study protocol and consent form were approved by the Committee on Human Research at the University of California, San Francisco. Subjects were included if they met DSM-IV criteria for combat-related PTSD as assessed using the Clinician Administered PTSD Scale (CAPS).[27] Subjects were excluded if they met alcohol or substance abuse criteria within the past 6 months, or lifetime criteria for schizophrenia, schizoaffective disorder, bipolar disorder, panic disorder, obsessive-compulsive disorder, or organic mental disorder as assessed by the Structured Clinical Interview for DSM-IV, Patient Edition.[28] Medical exclusion criteria included loud snoring, daytime sleepiness, or any history of brain disease or current systemic illness affecting central nervous system function. Subjects with a history of nefazodone or antipsychotic medication use in the past year were also excluded.

Procedure

The first phase of the study was a 2-week drug washout for psychoactive medication and laboratory screening for medical illness and urine toxicology. Subjects satisfying all study inclusion criteria were started on treatment with nefazodone, 50 mg/day. Medication was increased in weekly 100- or 200-mg increments to a target dosage ranging from 400 to 600 mg/day. The active treatment phase consisted of a 12-week trial. A flexible dosing strategy was utilized to provide nefazodone in the morning or evening, depending on the balance of arousing and sedating effects. The mean dose of nefazodone at stabilization was 570 mg/day (range, 500–600 mg/day). Compliance was assessed by pill count check. Concomitant psychosocial treatment was limited to ongoing therapy initiated prior to the trial. Newly initiated psychotherapy was deferred until the completion of the trial. No concurrent psychotropic or hypnotic medications were allowed during the course of the trial. Data were collected in 1999 and 2000.

Measures

Objective sleep quality was measured with ambulatory polysomnography (Oxford MR95 recorder, Oxford Instruments, Witney, United Kingdom) in the subject's home environment for 2 nights prior to treatment and 2 nights at the end of the 12-week trial. The primary analyses focused on the second night of polysomnography at both the baseline and end-of-trial recordings. The parameters recorded included an EEG at leads C3 and C4, left and right electro-oculograms (EOGs), submental electromyogram, and electrocardiogram in accordance with standardized guidelines.[29] The EEG and EOG leads were referenced to linked mastoids. An oximeter (Cricket, Respironics, Inc., Murrysville, Pa.) was used to screen for obstructive sleep apnea (OSA). The cutoff criterion for apnea was 10 desaturation events per hour in bed, which has been shown to have a sensitivity of 98% and specificity of 48% in detecting OSA.[30] All sleep was imported into Pass Plus (Delta Software, St. Louis, Mo.) analytic software and visually scored in 30-second epochs in accordance with Kales and Rechtschaffen.[29]

Sleep onset was defined as the first minute of 10 consecutive minutes of stage 2 sleep with no more than 2 intervening minutes of stage 1 sleep or time awake. REM periods were defined by at least 3 minutes of consecutive REM sleep with no less than 30 minutes of NREM sleep separating 2 REM periods. Sleep architecture was delin-

Table 1. Descriptive Statistics, Effect Sizes, and Paired t Test Results for Ratings of PTSD and Depressive Symptoms and Subjective Sleep Quality (N = 10)

Scale	Baseline Score Mean (SD)	Final Score Mean (SD)	Effect Size[a]	t	p (2-tailed)
CAPS	75.3 (9.9)	61.7 (15.4)	0.94	3.0	.016
IES-R	56.9 (11.9)	41.1 (15.2)	1.00	3.1	.012
PSQI global score	14.3 (2.9)	10.9 (2.7)	1.17	3.7	.005
Nightmares (IES-R)	3.5 (1.2)	2.1 (0.9)	1.43	4.3	.003
HAM-D	21.9 (6.1)	12.4 (7.9)	1.02	3.1	.015
BDI	26.7 (11.0)	20.6 (12.8)	0.63	2.0	.079
POMS					
Anger-hostility	25.2 (8.2)	17.4 (8.3)	0.65	1.9	.088
Tension-anxiety	22.0 (5.4)	14.0 (8.3)	1.24	3.7	.006

[a]Effect size is for baseline versus week 12; effect size equals the difference in means divided by the standard deviation of subjects' change scores.
Abbreviations: BDI = Beck Depression Inventory, CAPS = Clinician Administered PTSD Scale, HAM-D = Hamilton Rating Scale for Depression, IES-R = Impact of Event Scale-Revised, PSQI = Pittsburgh Sleep Quality Index, POMS = Profile of Mood States, PTSD = posttraumatic stress disorder.

eated as the percentage of time spent asleep in NREM stages 1 through 4 and stage REM. Sleep continuity was measured by calculating sleep maintenance, defined as the ratio of total time spent asleep divided by the total recording period between sleep onset and offset. An awakening was defined by EEG arousals lasting 30 seconds or longer. REM measures included REM percentage, REM activity (number of rapid eye movements), REM density (REM activity/minutes REM sleep), REM latency, and number of REM periods.

Delta sleep was analyzed by PAA using the Pass Plus analytic software. Integrated amplitude of 0.3 to 4.0 Hz activity per 30-second epoch was analyzed across all recorded sleep following the technique described by Feinberg and colleagues[31–32] and Travis et al.[33] Period amplitude analyses were conducted on all epochs of NREM and REM sleep. Epochs scored as wake were not included in these analyses. Movement artifact was visually tagged and not included in the analyses. Because sleep consists of recurring cycles of NREM and REM sleep throughout the night, we also analyzed delta sleep by NREM period.

Intrusion, avoidance, and arousal symptoms of PTSD were assessed by the CAPS[27] and participant self-report, utilizing the Impact of Event Scale-Revised (IES-R).[34] Depressive symptoms were assessed with the Hamilton Rating Scale for Depression[35] and the Beck Depression Inventory.[36] Subjective sleep quality was assessed with the global score of the Pittsburgh Sleep Quality Index.[37] Nightmares were indexed by an item assessing trauma-specific dreams in the IES-R. The Profile of Mood States[38] subscales were used as state-sensitive self-report measures of anger-hostility and tension-anxiety. All measures were administered at baseline and at the completion of the 12-week trial.

Data Analyses

Primary outcome analyses focus on stress-specific symptoms and subjective and objective measures of sleep quality. Descriptive data provide means and standard deviations of the outcome variable at baseline and at the conclusion of 12 weeks on medication. Effect size calculations and paired t tests were performed to determine the significance of changes with treatment.

RESULTS

All subjects completed a 12-week open-label trial of nefazodone (mean dose = 570 mg/day; range, 500–600 mg/day). The age range of our subjects was 45 to 63 years (mean ± SD = 54.1 ± 5.3 years). Five were white, 2 were African American, 2 were Asian American, and 1 was Native American. Subjects' education levels ranged from 12 to 17 years (mean = 14.6 ± 1.4 years). Most (7/10) met DSM-IV criteria for lifetime alcohol or substance abuse. Two subjects met criteria for current major depressive disorder.

At baseline, the subjects had high levels of PTSD and depressive symptoms and had substantially impaired subjective sleep quality. The assessment at the final phase (12 weeks) showed significant decreases in both self-reported and clinician-reported ratings of PTSD symptoms (Table 1). Nefazodone treatment resulted in a significant decrease in the clinician ratings of depression, but there was only a trend for a decrease in self-reported depressive symptoms. The medication also improved subjective global sleep quality and had a particularly robust impact on reducing nightmares. Treatment also was associated with a significant reduction in subjective tension-anxiety.

The effects of nefazodone therapy on visually scored sleep architecture are presented in Table 2. Nefazodone therapy resulted in a highly significant increase in total sleep time and sleep maintenance. There was a significant increase in minutes of stage 2 sleep and a trend for an increase in minutes of REM sleep. However, there were no significant increases in the percentage of any one specific sleep stage in relation to the others, suggesting that nefa-

Table 2. Effects of Nefazodone on Visually Scored Sleep Architecture in 10 PTSD Subjects

Measure	Baseline Mean (SD)	Week 12 Mean (SD)	Effect Size[a]	t	p (2-tailed)
Total sleep time, minutes	324 (75)	460 (56)	1.95	–5.5	.001
Sleep maintenance, %	71.3 (15.6)	91.7 (7.6)	1.11	–3.2	.016
Wake (minutes) after sleep onset	158 (137)	46 (45)	0.79	2.2	.061
Stage 1					
Minutes	24 (13)	19 (16)	0.29	0.8	.435
Percent	7.4 (3.2)	4.1 (3.8)	0.78	2.2	.064
Stage 2					
Minutes	165 (48)	256 (101)	1.17	–3.3	.013
Percent	50.9 (8.2)	54.6 (19.3)	0.26	–0.7	.492
Stage 3					
Minutes	28 (17)	44 (56)	0.38	–1.1	.322
Percent	9.6 (6.9)	10.2 (13.3)	0.08	–0.2	.824
Stage 4					
Minutes	14 (28)	24 (47)	0.41	–1.2	.280
Percent	4.4 (8.7)	6.2 (12.3)	0.30	–0.8	.430
Total delta sleep					
Minutes	42 (38)	69 (90)	0.41	–1.2	.284
Percent	14.0 (12.4)	16.4 (22.4)	0.18	–0.5	.631
Stage REM					
Minutes	84 (36)	108 (50)	0.83	–2.4	.051
Percent	25.1 (5.7)	23.0 (9.1)	0.44	1.2	.257
REM latency, minutes	157 (149)	95 (34)	0.42	1.2	.277
REM activity, minutes	358 (248)	435 (229)	0.74	–2.1	.075
REM density[b]	3.9 (1.5)	3.8 (1.0)	0.06	0.2	.870
Movement time, minutes	9 (9)	9 (6)	0.01	0.0	.989

[a]Effect size is for baseline versus week 12; effect size equals the difference in means divided by the standard deviation of subjects' change scores.
[b]REM density is measured by the total number of rapid eye movements/total number of minutes in REM sleep.
Abbreviation: PTSD = posttraumatic stress disorder.

Table 3. Effects of Nefazodone on Delta Sleep as Measured by Period Amplitude Analysis (PAA) in 10 PTSD Subjects

Measure	Baseline Mean (SD)	Week 12 Mean (SD)	Effect Size[a]	t	p (2-tailed)
PAA during total sleep (delta: 0.3–4.0 Hz)					
Integrated amplitude	126276 (48978)	202502 (56121)	2.14	–6.1	.001
Time in band	8832 (3276)	13832 (3393)	1.87	–5.3	.001
No. of half-waves	38419 (12722)	57103 (12182)	1.46	–4.1	.004
PAA by NREM period: integrated amplitude of delta (0.3–4.0 Hz)					
NREM1	44069 (28082)	60845 (27452)	0.75	–2.1	.070
NREM2	38896 (21723)	64890 (44262)	0.62	–1.7	.124
NREM3	25565 (13115)	48329 (29342)	1.22	–3.2	.018
NREM4	15310 (9280)	22816 (6215)	1.17	–2.9	.035
NREM5	16519 (6628)	19101 (10154)	0.62	–1.1	.394

[a]Effect size is for baseline versus week 12; effect size equals the difference in means divided by the standard deviation of subjects' change scores.
Abbreviations: NREM = non–rapid eye movement, PTSD = posttraumatic stress disorder.

zodone did not preferentially impact any particular aspect of visually determined sleep architecture.

The effects of nefazodone therapy on quantitative delta sleep as measured by PAA are presented in Table 3. Period amplitude analysis of delta sleep showed that nefazodone resulted in a substantial increase in delta sleep as measured by delta integrated amplitude, time in delta band, and number of half-waves. Analysis by NREM period showed that the NREM periods with a statistically significant increase in delta sleep were in the mid-portion of the night in NREM periods 3 and 4.

DISCUSSION

Nefazodone therapy in a sample of combat veterans with severe symptoms of PTSD resulted in a significant reduction in symptomatic distress, a substantial improvement in global sleep quality, and a reduction in nightmares. The polysomnography data demonstrate a significant increase in total sleep time and sleep continuity and a large increase in quantitative delta sleep. Despite a small sample size, the improvement in objective sleep quality was highly significant.

The data from both this study and the report by Gillin et al.[15] showed that nefazodone therapy led to improvement in PTSD symptoms and subjective sleep quality. However, the study by Gillin and colleagues, in contrast to ours, did not find improvement in polysomnographic sleep measures. We believe that the difference may be related to several factors. At baseline, our PTSD subjects had worse sleep continuity disturbances (71% sleep efficiency) than the subjects of Gillin et al. (85% baseline sleep efficiency). It is possible that our recruitment effort, which did include a focus on sleep, produced a sample with worse sleep disturbance at study entry. Another difference is that the mean dose of nefazodone in the Gillin et al. study was 441 mg/day compared with a mean of 570 mg/day in this study. It is possible that the higher dose accounted for the moderately higher sleep efficiency at end of trial (91% in our study) compared with 84% in the Gillin et al. study. Interestingly, the one polysomnographic measure that approached statistical significance in the Gillin et al. study was delta sleep percentage. In their study, mean ± SD delta sleep percentage went from 4.0 ± 1.4 at baseline to 2.8 ± 1.4 at week 2, 2.5 ± 0.9 at week 4, 9.0 ± 4.0 at week 8, and 16.8 ± 4.1 at week 12. Their time series analyses of the change in delta sleep showed that the effect of nefazodone did not reach statistical significance; however, this may be related to the lack of effect on delta sleep in the first 4 weeks of the trial.

The main difference in the 2 studies is that we employed PAA, a quantitative measure of delta sleep that increased the sensitivity of our measurement. Visual sleep scoring assigns a single numeric value to each epoch of sleep (e.g., stage 3) and does not account for the complexity of the sleep EEG across the night. It is possible for quantitative delta sleep to increase substantially without actually impacting visually scored sleep stages. For example, if quantitative delta sleep increases by 20% across the night, it is possible that the percentage of stages 3 and 4 may change very little. Our data suggest that quantitative measures of delta sleep are the most sensitive measures of polysomnographic change related to nefazodone therapy.

This study does have limitations that affect the generalizability of the findings. A randomized controlled trial (RCT) with a placebo condition would provide a more definitive test of the effect of nefazodone on symptomatic distress and subjective sleep quality. A controlled comparison of nefazodone with a different antidepressant that does not block 5-HT_2 receptors, such as a selective serotonin reuptake inhibitor, would provide stronger support for the hypothesis that 5-HT_2 blockade is important for improving sleep quality. Further, an RCT would account for any time-dependent effects on polysomnographic measures of sleep time, sleep continuity, and delta sleep. However, it is unlikely that a placebo condition would result in as large an effect on either total sleep time or delta sleep as was found in our study.

Given that sleep disturbances are a source of considerable distress for patients with chronic PTSD, nefazodone therapy may be a treatment to consider in this patient population. Like other agents that antagonize postsynaptic 5-HT_2 receptors, nefazodone leads to an increase in delta sleep. Current studies are underway that are examining if pharmacologic enhancement of delta sleep in this population leads to changes in nocturnal hormone secretory patterns associated with delta sleep release.[3,39]

Drug name: nefazodone (Serzone).

REFERENCES

1. Roszell DK, McFall ME, Malas KL. Frequency of symptoms and concurrent psychiatric disorder in Vietnam veterans with chronic PTSD. Hosp Community Psychiatry 1991;42:293–296
2. Woodward SH, Murburg MM, Bliwise DL. PTSD-related hyperarousal assessed during sleep. Physiol Behav 2000;70:197–203
3. Vgontzas AN, Mastorakos G, Bixler EO, et al. Sleep deprivation effects on the activity of the hypothalamic-pituitary-adrenal and growth axes: potential clinical implications. Clin Endocrinol 1999;51:205–215
4. Feinberg I. Changes in sleep cycle patterns with age. J Psychiatr Res 1974;10:283–306
5. Borbely AA, Achermann P. Homeostasis of human sleep and models of sleep regulation. In: Kryger MH, Roth T, Dement WC, eds. Principles and Practice of Sleep Medicine. Philadelphia, Pa: WB Saunders; 2000:377–390
6. Eison AS, Eison MS, Torrente JR, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990;26:311–315
7. 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
8. 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
9. 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
10. Hertzberg MA, Feldman ME, Beckham JC, et al. Open trial of nefazodone for combat-related posttraumatic stress disorder. J Clin Psychiatry 1998;59:460–464
11. Davidson JR, Weisler RH, Malik ML, et al. Treatment of posttraumatic stress disorder with nefazodone. Int Clin Psychopharmacol 1998;13: 111–113
12. Hidalgo R, Hertzberg MA, Mellman T, et al. Nefazodone in posttraumatic stress disorder: results from six open-label trials. Int Clin Psychopharmacol 1999;14:61–68
13. 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
14. Mellman TA, David D, Barza L. Nefazodone treatment and dream reports in chronic PTSD. Depress Anxiety 1999;9:146–148
15. Gillin JC, Smith-Vaniz A, Schnierow B, et al. An open-label, 12-week clinical and sleep EEG study of nefazodone in chronic combat-related posttraumatic stress disorder. J Clin Psychiatry 2001;62:789–796
16. Landolt HP, Meier V, Burgess HJ, et al. Serotonin-2 receptors and human sleep: effect of a selective antagonist on EEG power spectra. Neuropsychopharmacology 1999;21:455–466
17. Idzikowski C, Mills FJ, Glennard R. 5-Hydroxytryptamine-2 antagonist increases human slow wave sleep. Brain Res 1986;378:164–168
18. Borbely AA, Trachsel L, Tobler I. Effect of ritanserin on sleep stages and sleep EEG in the rat. Eur J Pharmacol 1988;156:275–278
19. Dijk DJ, Beersma DG, Daan S, et al. Effects of seganserin, a 5-HT2 antagonist, and temazepam on human sleep stages and EEG power spectra. Eur J Pharmacol 1989;171:207–218
20. Sharpley AL, Elliott JM, Attenburrow MJ, et al. Slow wave sleep in

humans: role of 5-HT2A and 5-HT2C receptors. Neuropharmacology 1994;33:467–471
21. 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
22. Vogal G, Cohen J, Mullis D, et al. Nefazodone and REM sleep: how do antidepressant drugs decrease REM sleep? Sleep 1998;21:70–77
23. Sharpley AL, Walsh AE, Cowen PJ. Nefazodone—a novel antidepressant—may increase REM sleep. Biol Psychiatry 1992;31:1070–1073
24. Ware JC, Rose FV, McBrayer RH. The acute effects of nefazodone, trazodone and buspirone on sleep and sleep-related penile tumescence in normal subjects. Sleep 1994;17:544–550
25. Armitage R. Microarchitectural findings in sleep EEG in depression: diagnostic implications. Biol Psychiatry 1995;37:72–84
26. Reynolds CF, Brunner D. Sleep microarchitecture in depression: commentary. Biol Psychiatry 1995;37:71
27. Blake DD, Weathers FW, Nagy LM, et al. The development of a clinician-administered PTSD scale. J Trauma Stress 1995;8:75–90
28. First MB, Spitzer RL, Gibbon M, et al. Structured Clinical Interview for DSM-IV-TR Axis I Disorders, Research Version, Patient Edition (SCID-I/P). New York, NY: Biometric Research, New York State Psychiatric Institute; 2001
29. Kales A, Rechtschaffen A. A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects. Bethesda, Md: US National Institute of Neuropsychological Diseases and Blindness, Neurological Information Network; 1968. National Institutes of Health publication 204
30. Sériès F, Marc I, Cormier Y, et al. Utility of nocturnal home oximetry for case finding in patients with suspected sleep apnea hypopnea syndrome. Ann Intern Med 1993;119:449–453
31. Feinberg I, Floyd TC, March JD. Effects of sleep loss on delta (0.3–3 Hz) EEG and eye movement density: new observations and hypotheses. Electroencephalogr Clin Neurophysiol 1987;67:217–221
32. Feinberg I, Floyd TC, March JD. Acute deprivation of the terminal 3.5 hours of sleep does not increase delta (0–3 Hz) electroencephalograms in recovery sleep. Sleep 1991;14:316–319
33. Travis F, Maloney T, Means M, et al. Acute deprivation of the terminal 4 hours of sleep does not increase delta (0–3 Hz) electroencephalograms: a replication. Sleep 1991;14:320–324
34. Weiss DS, Marmar CR. The Impact of Event Scale-Revised. In: Wilson JP, Keane TM, eds. Assessing Psychological Trauma and PTSD: A Practitioner's Handbook. New York, NY: Guilford Press; 1997:399–411
35. Hamilton M. Development of a rating scale for primary depressive illness. Br J Soc Clin Psychol 1967;6:278–296
36. Beck AT, Ward CH, Mendelson M, et al. An inventory for measuring depression. Arch Gen Psychiatry 1961;4:561–571
37. 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
38. McNair DM, Lorr M, Droppleman LF. Profile of Mood States Manual. San Diego, Calif: Education and Industrial Testing Service; 1992
39. Van Cauter E, Leproult R, Plat L. Age-related changes in slow wave sleep and REM sleep and relationship with growth hormone and cortisol levels in healthy men. JAMA 2000;284:861–868