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

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Background: Previous small trials have suggested that nefazodone does not suppress rapid-eye-movement (REM) sleep or increase REM latency in depressed patients, in contrast to fluoxetine. The effects of nefazodone and fluoxetine on sleep architecture and on clinician- and patient-rated sleep measures were directly compared in this 8-week, multicenter, double-blind, randomized, parallel-group study.

Method: Forty-four outpatients with moderate to severe, nonpsychotic major depressive disorder (DSM-III-R) and insomnia were randomly assigned to receive nefazodone (Days 1–7, 200 mg/day; Days 8–56, 400 mg/day) or fluoxetine (Days 1–56, 20 mg/day). Sleep measures were obtained at baseline, while patients were unmedicated, and at Weeks 2, 4, and 8 of treatment.

Results: In 43 evaluable patients (23 nefazodone, 20 fluoxetine), nefazodone and fluoxetine demonstrated similar antidepressant efficacy. All significant values were $p < .05$. Fluoxetine significantly decreased sleep efficiency and REM sleep and increased number of awakenings, Stage 1 sleep, and REM latency compared with baseline. In contrast, nefazodone significantly decreased percentage of awake and movement time and did not alter sleep efficiency or number of awakenings, Stage 1 or REM sleep, or REM latency compared with baseline. Nefazodone was associated with significantly less change from baseline for sleep efficiency, number of awakenings, percentage of awake and movement time, percentage of REM and Stage 1 sleep, and REM latency compared with fluoxetine. Both fluoxetine- and nefazodone-treated patients also showed significant improvement in some clinician- and patient-rated sleep disturbance scores, but nefazodone-treated patients improved to a significantly greater extent than fluoxetine-treated patients in most measures.

Conclusion: While nefazodone and fluoxetine showed equivalent antidepressant efficacy, more objective, subjective, and clinician-rated measures of sleep disturbance were improved during treatment with nefazodone than with fluoxetine. These results suggest that antidepressant effects of medications can occur independently of drug-induced changes in objective, subjective, and clinician-rated measures of sleep. Further studies, including parallel placebo-controlled comparisons with nefazodone, are needed to further test this hypothesis.

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Most antidepressant drugs suppress rapid-eye-movement (REM) sleep and increase REM latency.[1] In an extensive review of drug effects on REM sleep in patients with endogenous depression, Vogel and colleagues[2] reported that almost all of the 25 antidepressants examined are probable suppressors of REM sleep. Among the most potent of these is the serotonin selective reuptake inhibitor (SSRI) fluoxetine.[2–4] Recent studies involving depressed patients have shown that the administration of fluoxetine is associated not only with a decrease in the amount of REM sleep, but also with increases in the number of stage shifts and awakenings, the amount of Stage 1 sleep time, and REM latency.[3,4]

The antidepressant nefazodone has a pharmacologic profile that is distinct from that of tricyclic antidepressants, monoamine oxidase inhibitors, SSRIs, bupropion, and venlafaxine. Nefazodone is a potent 5-HT_2 receptor antagonist and an inhibitor of serotonin (5-HT) and norepinephrine reuptake.[5,6] These mechanisms of action are believed to be the basis of its antidepressant activity. With chronic administration, nefazodone has been shown to down-regulate 5-HT_2 receptors.[6] While nefazodone has little affinity for other neurotransmitter receptors, it does have affinity for α_1 receptors.[5,6]

Results from previous studies suggest that nefazodone does not suppress REM sleep or increase REM latency in

healthy subjects[7,8] or depressed patients.[9] Thus, although suppression of REM sleep has been proposed as the mechanism of action of antidepressant medication,[10] REM sleep suppression does not appear to be necessary for the antidepressant response to nefazodone.[9]

This double-blind, randomized study was designed to compare the effects of nefazodone and fluoxetine on sleep architecture and subjective sleep complaints in depressed outpatients with insomnia.

METHOD

This randomized, parallel-group study was conducted at four sites and consisted of a 1- to 4-week baseline phase, during which patients were unmedicated, and an 8-week, double-blind, antidepressant treatment phase. This article reports on one of three similar independent studies comparing nefazodone and fluoxetine. The other two studies will be analyzed and reported separately.

Patients

Outpatients, 21 to 55 years of age, who met DSM-III-R criteria for a nonpsychotic, moderate to severe major depressive disorder were included in this study. Diagnoses were made on the basis of the Structured Clinical Interview for DSM-III-R (SCID).[11] A minimum score of 18 on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D-17) was required for entry into the study. All patients were required to meet one of the following subjective criteria for a sleep disturbance: (1) difficulty in falling asleep on a nightly basis, (2) waking up during the night, or (3) inability to fall asleep again after waking during the night. Patients were excluded who engaged in shiftwork, and those with primary sleep disorders independent of affective disturbance, current general medical conditions, or with a history of psychoactive substance use disorder within 12 months prior to study entry were also excluded. In addition, patients with current DSM-III-R Axis I disorders in categories such as organic mental syndromes and disorders, bipolar disorder-depressed, and schizophrenia, delusional disorder, or psychotic disorders not classified elsewhere were excluded. Pregnant, lactating, or sexually active women who were not using an approved method of contraception were not eligible. All patients provided written informed consent before the start of the study. The study protocol, which was approved by the human review committees at the respective study centers, was carried out in accordance with the tenets of the Declaration of Helsinki.

Study Drug Administration

Each patient participated in a 1- to 4-week baseline phase, during which time they received no antidepressant drugs, to ensure that all eligibility criteria were met and that all relevant baseline data were recorded. Patients with a HAM-D-17 score of 18 or greater at the end of the baseline phase were randomly assigned to receive either nefazodone or fluoxetine for 8 weeks in a double-blind fashion using a double-dummy dosing scheme. The research design did not include a parallel, placebo-control group since this study was not designed primarily to determine the absolute antidepressant efficacy of either nefazodone or fluoxetine. Nefazodone 100 mg b.i.d. (100-mg tablets) was administered orally on Days 1 to 7, and the dosage was increased to 200 mg b.i.d. on Days 8 to 56. Fluoxetine 20 mg (20-mg capsule) was administered orally each morning throughout the study (Days 1 to 56). If clinically indicated, the dosage of the study drug could be increased (on a double-blind basis) to 500 mg/day for nefazodone and 40 mg/day for fluoxetine on Day 29.

Evaluation of Antidepressant Efficacy

The antidepressant efficacy of each study drug was evaluated at Weeks 1, 2, 3, 4, 6, and 8 (or at the time of early discontinuation) by using the HAM-D total score and the HAM-D depressed mood item (#1).

Safety and Tolerability Assessments

Throughout the study, adverse events were evaluated by the investigator in terms of incidence, duration, severity, and possible relationship to the study drug. Vital signs were measured at baseline and at Weeks 2, 4, 6, and 8, or at endpoint. Electrocardiographs, physical examinations, and clinical laboratory tests were performed at baseline and at endpoint.

EEG Recording Procedures

Polysomnographic recordings were collected over 2 consecutive nights at the end of the baseline phase and at Weeks 2, 4, and 8 of treatment. Recordings were made at each study center in a sleep laboratory and were sent to a central scoring site (University of California, San Diego) where they were scored without knowledge of study drug or dose. Patients maintained consistent sleep schedules with regular bed and rise times throughout the study. Electroencephalographic (EEG) recordings were collected from left central (C_3) electrodes. Monopolar, left, and right electrooculograms (EOG) and chin/cheek electromyograms (EMG) were also recorded. Bipolar, linked leg electrodes were also utilized.

The polysomnographic recordings were scored using the method of Rechtschaffen and Kales.[12] Sleep technicians were carefully trained and maintained high interrater reliability for scoring each sleep measure ($r \geq .85$). Sleep stage scores for 30-second epochs were entered into a data base using a computer data entry program and submitted to the Sleep Study Unit at the University of Texas Southwestern Medical Center at Dallas for computation of objective sleep parameters.

A number of polysomnographic variables were derived from the sleep stage–score data, including time of sleep onset, which was defined as the beginning of the first 10-minute segment after lights out containing at least 8 minutes of Stage 1 sleep or any other sleep stage. Also calculated were total time in bed (TIB), total sleep period (TSP), total sleep time (TST) within TSP, awake and movement time within TSP, and number of awakenings (≥ 30 seconds in duration). REM latency was defined as the interval between sleep onset and the first epoch of REM, including awake and movement time. The minutes and percentages at each sleep stage (1, 2, 3, 4, and REM) were also calculated using polysomnographic data. Sleep latency was measured as minutes from lights out to sleep onset. Sleep efficiency was calculated as the percentage of TIB spent asleep (TST/TIB) × 100.

Measurements of Sleep Disturbance

Aspects of sleep disturbance were evaluated using several psychometric rating scales, including the HAM-D sleep disturbance factor, composed of initial, middle, and delayed insomnia items. Initial, middle, and delayed insomnia refer to difficulty falling asleep after going to bed, difficulty staying asleep from midnight to 3 a.m., and early morning awakening, respectively. The 28-item Inventory for Depressive Symptomatology–Clinician-Rated (IDS-C) and the Inventory for Depressive Symptomatology–Self-Rated (IDS-SR)[13] were also used to assess sleep disturbance characteristics. Each inventory includes the items to assess sleep onset, midnocturnal and early morning insomnia, as well as hypersomnia (Items 1–4).

Statistical Methodology

For demographic and safety analyses, the total sample was comprised of all patients who were randomly assigned to treatment and received a dose of study drug. All patients who were randomly assigned to treatment, received a dose of study drug, and had at least one sleep or efficacy evaluation during treatment were included in the sleep and efficacy analyses, respectively. Statistical analyses of sleep parameters were based on this intent-to-treat sample.

Polysomnographic parameters, as well as the 17-item HAM-D and the sleep items and the sleep factors of the 28-item IDS-C and the IDS-SR, were analyzed using an analysis of variance (ANOVA) with consideration of treatment, study center, and treatment-by-study center interaction effects. These analyses were used to assess differences between treatment groups in change from baseline at endpoint. For all efficacy parameters, the last observation carried forward (LOCF) endpoint data set includes patient data recorded at the Week 8 visit or, if no observation was recorded at that week's visit, data that were carried forward from the previous visit.

Polysomnographic parameters were based on mean data obtained on 2 consecutive nights at each evaluated week. For key sleep parameters (REM latency, REM and Stage 1 sleep, awake and movement time, number of awakenings, and sleep latency), data obtained from recordings of Night 2 only were also analyzed to corroborate the analysis based on the mean of 2 nights. The LOCF data set was used at endpoint for polysomnographic data; for all other visits, observations at each scheduled visit were used.

The reported p values are two-tailed tests of significance rounded to two decimal places. Values less than or equal to .05 were considered statistically significant.

RESULTS

Forty-four patients were enrolled in the study and received nefazodone (N = 24) or fluoxetine (N = 20) in a double-blind fashion. A total of 43 patients were evaluable for efficacy: 23 in the nefazodone-treatment group and 20 in the fluoxetine-treatment group. Of the 44 patients who entered the study and received study medication, 36 completed the study and 8 discontinued early. Four patients (17%) receiving nefazodone and 3 (15%) receiving fluoxetine discontinued treatment because of adverse events. One patient receiving nefazodone was considered unreliable and was withdrawn from the study.

At endpoint (last observation at or before Week 8), the mean modal daily dose was 434.8 mg/day for nefazodone and 34.0 mg/day for fluoxetine.

Patient Demographic Characteristics

The demographic characteristics of the treatment groups are shown in Table 1. The two groups did not differ significantly with respect to demographic characteristics and psychiatric and psychotropic medication treatment history. Specifically, both treatment groups were similar in terms of previous history of depression, age at onset of first depressive episode, and previous use of antidepressant drugs.

The two treatment groups had similar ratings for baseline HAM-D scores for initial, middle, and delayed insomnia, with a median rating of 2 for initial and middle insomnia and 1 for delayed insomnia (Table 2). No patient was rated as "absent" (score of 0) on all three sleep disturbance items at baseline.

Antidepressant Efficacy and Tolerability

Both treatment groups showed similar improvement in depressive symptoms. This was evidenced by the change from baseline on the HAM-D-17 total score and the HAM-D depressed mood item score at endpoint. Baseline mean ± SE total scores for the HAM-D-17 were 22.9 ± 0.62 and 23.2 ± 0.66 and the values for mean change from baseline at endpoint were –11.5 ± 1.41 and

Table 1. Patient Demographic Characteristics at Study Entry*

Variable	Nefazodone N = 24	Fluoxetine N = 20
Age (y)		
Mean ± SE	35.3 ± 1.8	36.7 ± 1.9
Median (range)	35 (21–55)	38 (25–53)
Sex, N (%)		
Men	8 (33)	6 (30)
Women	16 (67)	14 (70)
Race, N (%)		
White	15 (63)	15 (75)
Black	4 (17)	1 (5)
Hispanic	5 (21)	1 (5)
Asian	0 (0)	3 (15)
Marital status, N (%)		
Married	9 (38)	4 (20)
Never married	11 (46)	13 (65)
Separated/divorced	4 (17)	2 (10)
Widowed	0 (0)	1 (5)
Weight (lb)		
Mean ± SE	156 ± 5.8	165 ± 9.4
Median (range)	152 (102–204)	147 (123–300)
HAM-D total score,		
Mean ± SE	22.9 ± 0.62	23.2 ± 0.66
Number of prior depressive episodes		
Mean ± SE	9.1 ± 4.3	8.2 ± 4.8
Median (range)	2 (0–99)	3 (0–99)
Age at onset of first depressive episode (y)		
Mean ± SE	24.1 ± 2.1	22.2 ± 1.8
Median (range)	23 (11–54)	20 (12–39)
Previous antidepressant use, N (%)		
Yes	10 (42)	10 (50)
No	14 (58)	10 (50)

*HAM-D = Hamilton Rating Scale for Depression; SE = standard error.

Table 2. Severity of Insomnia at Baseline Based on HAM-D Sleep Items*

HAM-D Item	Nefazodone N = 24	Fluoxetine N = 20
Item 4 (initial insomnia)		
Mean ± SE	1.3 ± 0.2	1.5 ± 0.2
Median (range)	2 (0–2)	2 (0–2)
Not recorded	1	0
Item 5 (middle insomnia)		
Mean ± SE	1.3 ± 0.2	1.5 ± 0.1
Median (range)	2 (0–2)	2 (0–2)
Not recorded	1	0
Item 6 (delayed insomnia)		
Mean ± SE	1.1 ± 0.2	1.1 ± 0.2
Median (range)	1 (0–2)	1 (0–2)
Not recorded	1	0

*Scores: 0 = absent, 1 = mild, 2 = obvious; HAM-D = Hamilton Rating Scale for Depression; SE = standard error.

Table 3. Effects of Nefazodone and Fluoxetine on Sleep Consolidation

Sleep Parameter	Baseline Mean	Baseline SE	Endpoint Mean	Endpoint SE	Comparison of Mean Change From Baseline at Endpoint[a] Mean	Comparison of Mean Change From Baseline at Endpoint[a] SE
Sleep efficiency[b] (%)						
Nefazodone (N = 23)	87.0	1.36	87.3	1.83	0.2	1.73
Fluoxetine (N = 18)	83.6	1.92	78.8	1.97*	–4.8	1.66††
Number of awakenings (≥ 30 sec)						
Nefazodone	24.6	2.16	23.3	2.04	–1.3	1.52
Fluoxetine	21.3	1.48	29.4	1.90*	8.1	2.75†
% Awake and movement time in TSP[c]						
Nefazodone	7.8	1.22	5.7	0.81**	–2.1	0.88
Fluoxetine	9.8	1.57	12.0	1.30	2.2	1.52†

[a]p Values based on an ANOVA model adjusted for study center.
[b](Total sleep time/time in bed) × 100.
[c]TSP = total sleep period.
*p ≤ .01 compared with baseline; **p ≤ .05 compared with baseline;
†p ≤ .01 compared with nefazodone change from baseline;
††p ≤ .05 compared with nefazodone change from baseline.

–10.3 ± 1.35 (95% confidence interval for the difference between treatments, –2.5 to 5.3; ANOVA) for the nefazodone and fluoxetine treatment groups, respectively. The values for mean change from baseline at endpoint on the depressed mood item score were –1.4 ± 0.28 and –1.1 ± 0.18 for nefazodone- and fluoxetine-treated patients, respectively. Neither comparison was statistically significant.

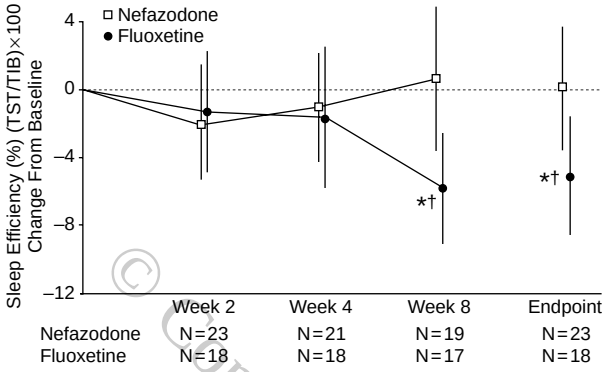
Treatment groups did not differ in the overall incidence or severity of adverse events. The most frequently occurring adverse events (occurring in ≥ 10% of patients) in those receiving nefazodone were headache, nausea, and dry mouth. In patients receiving fluoxetine, the most frequently occurring adverse events were headache, dry mouth, and somnolence.

Effects on Sleep

Sleep consolidation. The effects of nefazodone and fluoxetine on objective sleep consolidation measurements are shown in Table 3. At endpoint, patients receiving nefazodone tended to demonstrate decreased awake and movement time, but no change in sleep efficiency or number of awakenings compared with baseline was observed. In contrast, patients receiving fluoxetine demonstrated a significant increase in number of awakenings and reduced sleep efficiency compared with baseline. Compared with baseline scores, the fluoxetine treatment group showed significantly greater decrements in three sleep consolidation parameters—sleep efficiency, number of awakenings, and percentage of awake and movement time—than the nefazodone treatment group.

Mean change from baseline values for sleep efficiency over the course of treatment are illustrated in Figure 1. In nefazodone-treated patients, sleep efficiency did not change from baseline (87.0%) to endpoint (87.3%). Sleep efficiency, however, was significantly worsened in fluoxetine-treated patients from baseline (83.6%) to Week 8 and at endpoint (78.8%) ($p \leq .01$). The difference between treatment groups in change from baseline scores was significant at Week 8 and at endpoint (LOCF) ($p \leq .05$).

Figure 1. Effects of Nefazodone and Fluoxetine on Sleep Efficiency at Weeks 2, 4, 8, and at Endpoint[a]



[a]Last observation at or before Week 8. Mean change from baseline, 95% confidence intervals. TST = total sleep time; TIB = time in bed.
*p ≤ .01 compared with baseline.
†p ≤ .05 compared with nefazodone.

Sleep architecture. The effects of nefazodone and fluoxetine on polysomnographic measures of sleep architecture are shown in Table 4. Fluoxetine-treated patients exhibited increased Stage 1 sleep, reduced total REM sleep (both minutes/night and percentage of TSP), and increased REM latency compared with baseline. In contrast, patients receiving nefazodone demonstrated no statistically significant changes from baseline in any of these parameters. Differences between the nefazodone and fluoxetine treatment groups in percentage of Stage 1 and REM sleep and REM latency were statistically significant ($p \leq .01$). These effects resulted from a significantly greater reduction of absolute REM sleep in the fluoxetine group compared with the nefazodone group (mean change from baseline: nefazodone, 1.8 min/night; fluoxetine, –16.1 min/night; $p \leq .05$) rather than from significant changes in TSP. TSP remained unchanged over the course of treatment for both groups.

Figures 2, 3, and 4 illustrate the effects of nefazodone and fluoxetine on Stage 1 sleep, REM sleep, and REM latency over the course of treatment. Fluoxetine-treated patients demonstrated a significant increase in percentage of Stage 1 sleep at Weeks 4 and 8 and at endpoint compared with baseline, while the nefazodone group showed minimal change in percentage of Stage 1 sleep from baseline throughout treatment (6.9% at baseline vs. 6.3% at endpoint) (Figure 2). Patients treated with fluoxetine showed a significantly greater change from baseline at all time points compared with patients treated with nefazodone ($p \leq .01$).

Patients receiving nefazodone showed no consistent change in the percentage of REM sleep (Figure 3) or in REM latency (Figure 4) compared with baseline over time. In contrast, patients receiving fluoxetine exhibited significant consistent REM sleep suppression, as evidenced by decreased percentage of REM sleep in TSP

Table 4. Effects of Nefazodone and Fluoxetine on Sleep Architecture

	Baseline		Endpoint		Comparison of Mean Change From Baseline at Endpoint[b]	
Sleep Parameter[a]	Mean	SE	Mean	SE	Mean	SE
Stage 1 (% of TSP)						
Nefazodone (N = 23)	6.9	0.59	6.3	0.46	–0.6	0.44
Fluoxetine (N = 18)	7.1	0.60	11.6	1.01*	4.5	1.01†
Stage 2 (% of TSP)						
Nefazodone	53.8	1.86	56.2	1.66**	2.5	1.00
Fluoxetine	53.2	1.32	54.6	1.17	1.4	1.33
Stages 3 and 4 (% of TSP)						
Nefazodone	11.3	1.58	10.7	1.91	–0.6	1.08
Fluoxetine	10.4	1.52	6.9	0.97**	–3.5	1.33
REM (% of TSP)						
Nefazodone	20.2	0.94	21.0	0.96	0.8	0.99
Fluoxetine	19.4	0.75	14.8	1.63*	–4.6	1.52†
REM sleep latency (min)						
Nefazodone	81.5	4.27	72.4	4.86	–9.1	6.06
Fluoxetine	83.4	8.25	155.9	14.23*	72.5	17.90†
Sleep latency (min)						
Nefazodone	22.0	3.35	29.3	7.35	7.3	7.03
Fluoxetine	27.7	6.06	36.5	8.47	8.8	8.19

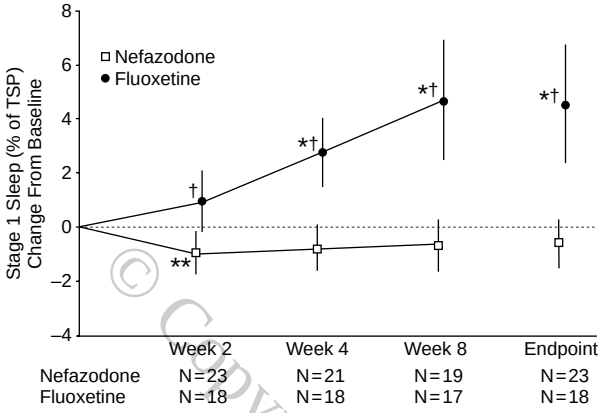
[a]TSP = total sleep period; REM = rapid eye movement.
[b]p Values based on an ANOVA model adjusted for study center.
*p ≤ .01 compared with baseline; **p ≤ .05 compared with baseline;
†p ≤ .01 compared with nefazodone change from baseline.

($p \leq .01$), and increased REM latency ($p \leq .01$) at all time points. The difference between treatment groups in change from baseline for percentage of REM sleep in TSP and REM latency were statistically significant at all time points (except Week 4 for percentage of REM sleep).

Sleep disturbance assessments. The effects of nefazodone and fluoxetine on sleep disturbance items of the HAM-D and on the four sleep items of the clinician- and self-rated IDS are shown in Tables 5–7. Compared with baseline, treatment with nefazodone and fluoxetine was associated with significantly improved scores on the Sleep Disturbance Factor and the initial, middle, and delayed insomnia items of the HAM-D. Nefazodone showed significantly greater improvement in the HAM-D total Sleep Disturbance Factor score (defined as the sum of initial, middle, and delayed insomnia items) compared with fluoxetine, with change from baseline values of –2.5 for nefazodone and –1.5 for fluoxetine ($p \leq .05$), and also in the delayed insomnia item score, with change from baseline values of –0.7 for nefazodone and –0.3 for fluoxetine ($p \leq .05$) (Table 5).

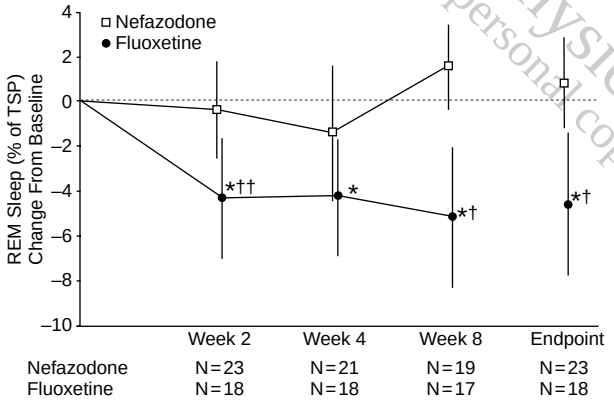
Compared with baseline, treatment with nefazodone and fluoxetine was associated with significantly improved scores on the Falling Asleep and Sleep During the Night items of the IDS-C and IDS-SR and the total sleep factor score for the IDS-C (Tables 6 and 7). Nefazodone was also associated with significantly improved scores on the Waking-Up-Too-Early items of the IDS-C and IDS-SR and the total sleep factor score for the IDS-SR.

Figure 2. Effects of Nefazodone and Fluoxetine on % Stage 1 Sleep at Weeks 2, 4, 8, and at Endpoint[a]



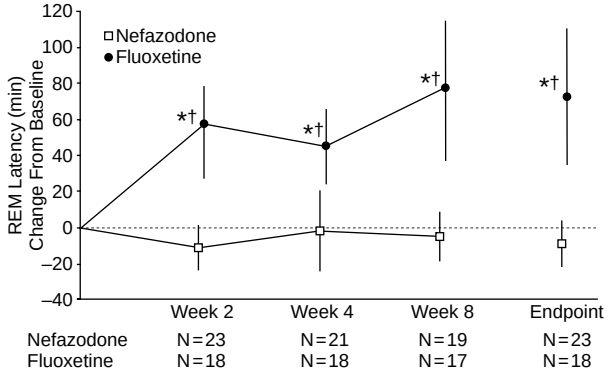
[a]Last observation at or before Week 8. Mean change from baseline, 95% confidence intervals. TSP = total sleep period.
*p ≤ .01 compared with baseline.
**p ≤ .05 compared with baseline.
†p ≤ .01 compared with nefazodone.

Figure 3. Effects of Nefazodone and Fluoxetine on % REM Sleep at Weeks 2, 4, 8, and at Endpoint[a]



[a]Last observation at or before Week 8. Mean change from baseline, 95% confidence intervals. TSP = total sleep period.
*p ≤ .01 compared with baseline.
†p ≤ .01 compared with nefazodone.
††p ≤ .05 compared with nefazodone.

Figure 4. Effects of Nefazodone and Fluoxetine on REM Latency at Weeks 2, 4, 8, and at Endpoint[a]



[a]Last observation at or before Week 8. Mean change from baseline, 95% confidence intervals.
*p ≤ .01 compared with baseline.
†p ≤ .01 compared with nefazodone.

Table 5. Effects of Nefazodone and Fluoxetine on Sleep Disturbance Items of the HAM-D

	Baseline		Endpoint		Comparison of Mean Change From Baseline at Endpoint[b]	
HAM-D Score[a]	Mean	SE	Mean	SE	Mean	SE
Sleep disturbance factor[c]						
Nefazodone (N = 23)	3.7	0.32	1.2	0.33*	–2.5	0.30
Fluoxetine (N = 20)	4.1	0.25	2.6	0.40*	–1.5	0.36†
Initial insomnia item						
Nefazodone	1.3	0.18	0.4	0.14*	–0.9	0.17
Fluoxetine	1.5	0.18	0.8	0.19*	–0.7	0.20
Middle insomnia item						
Nefazodone	1.3	0.16	0.4	0.14*	–0.9	0.17
Fluoxetine	1.5	0.14	1.0	0.20**	–0.5	0.21
Delayed insomnia item						
Nefazodone	1.1	0.16	0.4	0.14*	–0.7	0.18
Fluoxetine	1.1	0.18	0.9	0.13**	–0.3	0.13†

[a]HAM-D = Hamilton Rating Scale for Depression.
[b]Analysis using LOCF data set; p values based on an ANOVA model adjusted for study center.
[c]Sum of scores for three items.
*p ≤ .01 compared with baseline; **p ≤ .05 compared with baseline;
†p ≤ .05 compared with nefazodone change from baseline.

Patients treated with nefazodone showed significantly greater improvement on the Waking-Up-Too-Early items and the total sleep factor scores of the IDS-C and IDS-SR and on the Falling Asleep item of the IDS-SR compared with fluoxetine.

DISCUSSION

Nefazodone and fluoxetine demonstrated similar antidepressant efficacy compared with baseline measures of depression in this study of outpatients with major depressive disorder and insomnia. The two drugs, however, had dramatically different effects on both objective, clinician-rated, and patient-rated sleep measures. Nefazodone was associated with superior sleep quality compared with fluoxetine, as assessed by both clinician and patients on sleep items of the HAM-D and the IDS. Fluoxetine disturbed objective sleep architecture, while nefazodone improved it. Nefazodone significantly reduced percentage of awake and movement time within the TSP compared with baseline. Nefazodone did not reduce sleep efficiency or alter sleep latency, percentage of Stage 1 sleep, REM sleep, or REM latency compared with baseline. Nefazodone significantly improved a number of sleep quality measures to a greater extent than fluoxetine. These included the Sleep Disturbance Factor and delayed insom-

Table 6. Effects of Nefazodone and Fluoxetine on Sleep Items of the Inventory for Depressive Symptomatology–Clinician-Rated (IDS-C)

	Baseline		Endpoint		Comparison of Mean Change From Baseline at Endpoint[a]	
IDS-C Item	Mean	SE	Mean	SE	Mean	SE
Falling asleep						
Nefazodone (N = 23)	1.8	0.23	0.4	0.19*	–1.3	0.26
Fluoxetine (N = 20)	1.8	0.26	0.9	0.23*	–1.0	0.28
Sleep during the night						
Nefazodone	2.4	0.16	0.9	0.20*	–1.5	0.24
Fluoxetine	2.6	0.15	1.7	0.23*	–0.9	0.24
Waking up too early						
Nefazodone	1.3	0.24	0.4	0.16*	–0.9	0.25
Fluoxetine	1.2	0.27	1.0	0.22	–0.2	0.25†
Hypersomnia						
Nefazodone	0.2	0.08	0.4	0.14	0.3	0.14
Fluoxetine	0.3	0.10	0.6	0.15	0.3	0.15
Total sleep factor[b]						
Nefazodone	5.7	0.38	2.2	0.42*	–3.5	0.41
Fluoxetine	5.8	0.46	4.2	0.54*	–1.6	0.55†

[a]Analysis using LOCF data set; p values based on an ANOVA model adjusted for study center.
[b]Sum of scores for four items.
*p ≤ .01 compared with baseline;
†p ≤ .01 compared with nefazodone change from baseline.

Table 7. Effects of Nefazodone and Fluoxetine on Sleep Items of the Inventory for Depressive Symptomatology–Self-Rated (IDS-SR)

	Baseline		Endpoint		Comparison of Mean Change From Baseline at Endpoint[a]	
IDS-SR Item	Mean	SE	Mean	SE	Mean	SE
Falling asleep						
Nefazodone (N = 23)	1.9	0.21	0.6	0.16*	–1.3	0.22
Fluoxetine (N = 20)	1.5	0.22	1.0	0.22**	–0.5	0.22†
Sleep during the night						
Nefazodone	2.1	0.19	1.2	0.21*	–0.9	0.26
Fluoxetine[b]	2.4	0.18	1.8	0.20**	–0.6	0.23
Waking up too early						
Nefazodone	1.4	0.23	0.4	0.16*	–1.0	0.25
Fluoxetine	1.1	0.25	1.0	0.25	–0.2	0.33††
Hypersomnia						
Nefazodone	0.3	0.18	0.6	0.17	0.3	0.21
Fluoxetine	0.6	0.18	0.6	0.15	0.0	0.19
Total sleep factor[c]						
Nefazodone	5.8	0.46	2.8	0.46*	–3.0	0.52
Fluoxetine[b]	5.6	0.47	4.4	0.47	–1.2	0.58††

[a]Analysis using LOCF data set; p values based on an ANOVA model adjusted for study center.
[b]N = 19.
[c]Sum of scores for four items.
*p ≤ .01 compared with baseline; **p ≤ .05 compared with baseline;
†p ≤ .01 compared with nefazodone change from baseline;
††p ≤ .05 compared with nefazodone change from baseline.

nia item of the HAM-D; the Waking-Up-Too-Early and Total Sleep Factor on the IDS-C; and the Falling Asleep, Waking-Up-Too-Early, and Total Sleep Factor on the IDS-SR. In contrast, fluoxetine reduced sleep efficiency and percentage of Stages 3 and 4 sleep, increased percentage of Stage 1 sleep and number of awakenings, prolonged REM latency, and suppressed total REM sleep compared with baseline. Compared with nefazodone-induced changes, the fluoxetine-induced changes from baseline values were statistically significant for sleep efficiency, percentage of Stage 1 and REM sleep, and REM latency. There was no change in TSP over the course of treatment for either group.

Given that some investigators have reported differences between second night results and the mean of 2 nights in the sleep laboratory, we examined whether overall results were affected by the use of the mean of 2 nights or Night 2 data only. The overall effects of nefazodone and fluoxetine on sleep were not changed by the use of these different measures.

Although we observed significant differences between treatments on the sleep items of the psychometric scales, it should be noted that this study was not designed to detect statistically significant differences in the clinician- and patient-rated sleep disturbance items. Future studies with a larger number of patients will be required to better statistically assess the subjective effects of treatment on sleep disturbance.

Furthermore, as noted in the Method section, this study was not designed to compare the absolute clinical efficacy of either nefazodone or fluoxetine against a parallel, placebo-control group. While it is possible that the patients in the two treatment groups improved from baseline independently of pharmacologic effects, this possibility is unlikely. This caveat is important, however, in understanding the theoretical importance of our observation that the two drugs had opposite effects on sleep measures but similar antidepressant benefits. The significance of this "disconnect observation" would be greatly diminished if the clinical benefits of these two drugs resulted from nonpharmacologic factors during the course of the study. Another study with a parallel placebo group would be desirable to explore these issues more rigorously. An interesting and important question remains to be answered, namely, why did the patients in both groups experience similar clinical improvement from baseline for both subjective sleep and antidepressant effects when objective measures of sleep improved in the nefazodone group and worsened in the fluoxetine group?

The effects of nefazodone on sleep architecture reported in this double-blind study confirm the observations made in previous open-label studies with nefazodone. Armitage and colleagues[9] investigated the effects of nefazodone 400 to 600 mg/day for 4 to 8 weeks on sleep architecture in 10 outpatients with major depression. In support of results of the present study, nefazodone decreased arousals and wakefulness during sleep and did not increase REM latency or suppress REM sleep. A recent study of seven healthy volunteers, with no history of psychiatric disorder, demonstrated that nefazodone 100 mg twice daily for 7 days significantly

increased REM sleep ($p < .03$).[8] In contrast, treatment with fluoxetine has been associated with suppression of REM sleep and an increase in Stage 1 sleep and REM latency.[3,4,14]

Most antidepressant drugs suppress REM sleep. The suppression of REM sleep has been postulated to contribute to the mechanism of antidepressant action.[10] Suppression of REM sleep, however, is clearly not the mechanism by which nefazodone exerts its antidepressant effect. Nefazodone has demonstrated antidepressant efficacy comparable to other medications that do reduce the amount of REM sleep, including imipramine in double-blind, randomized clinical trials,[15–17] as well as fluoxetine in this study. In addition, several other effective antidepressants may not suppress REM sleep, including iprindole, trimipramine, amineptine, and bupropion.[2,18]

In conclusion, nefazodone and fluoxetine were equally effective in treating depression in outpatients with nonpsychotic major depressive disorder and complaints of insomnia. Both drugs were safe and well tolerated. In comparison to fluoxetine, however, nefazodone was associated with greater improvement in subjective and objective measures of sleep. In particular, nefazodone had minimal effects on REM sleep. Nefazodone, therefore, may provide clinical antidepressant benefits without objective sleep disruption compared with fluoxetine in this population of patients. Subjective insomnia and hypersomnia have been reported as common side effects with fluoxetine and other SSRIs.[19,20]

As mentioned earlier, this article is one of three similar reports of independent but similar studies. Once all the data are analyzed and summarized, a final report will be prepared on the overall results of the three studies.

It would also be of interest to assess whether objective polysomnographic measures correlate with clinician ratings and subjective patient ratings of sleep improvement in a larger sample of patients. If improved sleep is consistently associated with nefazodone, it will be interesting to determine whether patient compliance and acceptance of antidepressant treatment are also enhanced.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), imipramine (Tofranil and others), nefazodone (Serzone), trimipramine (Surmontil), venlafaxine (Effexor).

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