A Double-Blind, Placebo-Controlled Trial of Nefazodone in the Treatment of Patients Hospitalized for Major Depression

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Background: There are few published placebo-controlled clinical trials demonstrating the efficacy of the newer antidepressants in markedly or severely depressed hospitalized patients. This study demonstrates the efficacy of nefazodone compared with placebo in the treatment of patients hospitalized for major depression.

Method: Nefazodone and placebo treatment were compared in a 6-week trial of 120 patients hospitalized for DSM-III-R diagnosed major depression (without psychosis) at 2 study centers. Efficacy was evaluated using standard psychiatric rating scales, and patients were monitored for safety.

Results: Nefazodone treatment resulted in a significant reduction ($p < .01$) of the 17-item Hamilton Rating Scale for Depression (HAM-D-17) total score compared with placebo from the end of the first treatment week through the end of the study (–12.2 nefazodone vs. –7.7 placebo). At the end of the trial, significantly more nefazodone-treated patients (50%) than placebo-treated patients (29%) had responded, as indicated by their Clinical Global Impressions-Improvement score ($p = .021$) or by a ≥ 50% reduction in their HAM-D-17 scores ($p = .017$). Significantly more patients treated with nefazodone (36%) than placebo-treated patients (14%) had a HAM-D-17 score ≤ 10 at the end of treatment ($p = .004$). Significant treatment differences ($p < .01$) in favor of nefazodone were also seen in the Montgomery-Asberg Depression Rating Scale; the HAM-D retardation, anxiety, and sleep disturbance factors; and HAM-D item 1 (depressed mood). Patients with dysthymia in addition to major depression also showed significant improvement ($p < .05$) when treated with nefazodone, with significant differences in response rates seen as early as week 2 and through the end of the trial. The mean nefazodone dose was 491 mg/day at the end of week 2 and 503 mg/day at the end of treatment. Nefazodone was well tolerated, and the number of patients discontinuing owing to adverse events was small, with no significant safety issues noted in either treatment group. Fewer nefazodone-treated than placebo-treated patients discontinued owing to lack of efficacy.

Conclusion: Nefazodone was superior to placebo in the treatment of marked to severe major depression in patients requiring hospitalization. The clinical benefit of nefazodone was evident as early as the first week of treatment as judged by several measures of efficacy, with significant differences from placebo sustained throughout the trial.

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The demonstration of the efficacy of a new antidepressant in hospitalized patients is both important and challenging. Hospitalized patients are more severely depressed and have more potential for suicide than outpatients.[1] In addition, patients hospitalized for depression may represent individuals for whom previous psychotherapy or pharmacotherapy or both have not been effective. Since hospitalization itself can be a potent therapeutic intervention in the course of a depressive episode,[2] it is important to include a placebo control in clinical studies of antidepressants in the hospital setting.[1,3–5] The use of a placebo serves to control for the beneficial effects of hospitalization or other circumstances surrounding the care of depressed patients as well as the variability of the course of the illness.[1]

Many published studies of the newer antidepressants in hospitalized depressed patients lack a placebo comparator. The efficacy of many of the serotonin selective reuptake inhibitors (SSRIs) in the hospital setting has been reported only in comparison with another antidepressant drug.[6–10] There have been only a few published placebo-controlled clinical studies demonstrating the efficacy of SSRIs or other newer antidepressants in the hospital setting: fluvoxamine was superior to placebo and imipramine in a 6-week single-site trial,[11] venlafaxine was superior to placebo in a 4-week multicenter trial,[12,13] and mirtazapine was reported to be superior to placebo in a mixed population of inpatients and outpatients in 1 center of a multicenter trial.[14] Paroxetine resulted in no statistically significant improvement compared with placebo.[15]

Nefazodone is an antidepressant drug with a mechanism of action that distinguishes it from other antidepres-

sants, including the SSRIs.[16,17] Nefazodone potently antagonizes 5-HT_2 receptors and inhibits both serotonin and norepinephrine reuptake[16] while lacking an affinity for muscarinic cholinergic and H_1-histaminic receptors.[17]

An early study in 45 depressed outpatients demonstrated significant improvement following treatment with nefazodone compared with placebo and improvement comparable to that seen with imipramine.[18] In an 8-week, multicenter, double-blind, placebo-controlled study of 283 outpatients with major depression of at least 1 month's duration,[19] nefazodone was significantly better than placebo. In a similar 6-week clinical trial of 180 patients,[20] nefazodone was also found to be significantly superior to placebo treatment. In both of these studies,[19,20] the response rates in the nefazodone and active control (imipramine) groups were nearly identical, with nefazodone having a slight numerical advantage. Similar results were obtained in another placebo-controlled outpatient study with nefazodone and imipramine in which the response rate in the nefazodone treatment group was significantly greater than in the placebo treatment group and virtually identical to that in the imipramine treatment group.[21] In a trial of 2 dose ranges of nefazodone (mean doses = 239 and 392 mg/day at the end of the trial) compared with placebo, the response rate in the higher dose range treatment group was significantly greater than in the placebo group.[22] In other outpatient studies, nefazodone has been shown to have antidepressant response rates equivalent to those of the SSRIs paroxetine,[23] sertraline,[24] and fluoxetine.[25]

Ours is the first study reporting the results of the treatment of nefazodone in comparison with placebo in patients hospitalized for major depression.

METHOD

Study Design and Patient Population

This double-blind, randomized, parallel-group, 6-week study, conducted at 2 sites, was preceded by a 1- to 4-week drug-free baseline period. Patients were women (surgically sterile or practicing birth control with a negative pregnancy test result at baseline) and men at least 18 years of age. Participation in the trial required hospitalization. To be hospitalized, patients had to be at risk for suicide, not responsive to outpatient treatment, unable to comply with an outpatient treatment plan, or acutely and seriously impaired in their social, occupational, or familial milieu. All patients were diagnosed as having DSM-III-R major depression, single episode or recurrent, moderate to severe, with or without melancholia.[26] Patients were excluded from the study if they were diagnosed with bipolar disorder, a concurrent organic mental disorder, or psychosis or had a diagnosis of any significant psychoactive substance abuse disorder within 6 months prior to the beginning of the baseline phase. The last week of the baseline period was spent in the hospital. At the end of the baseline period, if any patient's score on the 17-item Hamilton Rating Scale for Depression (HAM-D-17) was less than 20 or if the patients were determined to no longer require hospitalization, they were excluded from the study. Eligible patients remained in the hospital for at least the first week of double-blind treatment, after which they could be discharged at the discretion of the investigator and treated as outpatients, with weekly visits scheduled for the duration of the trial. Patients in both the placebo and nefazodone treatment groups were hospitalized for an average of 26 days. The trial was conducted in accordance with the tenets of the Declaration of Helsinki, and all patients provided Internal Review Board–approved written informed consent.

Medication

The dosing regimen and intervals between dose titrations were individualized for each patient. Medication was started as 1 or 2 placebo or 100-mg nefazodone tablets daily, increasing by 1 tablet every 1 to 4 days to attain a dose of 2 tablets b.i.d. (400 mg/day of nefazodone) by the end of the first or second week of treatment. Then, if a patient did not have dose-limiting side effects, dosage could be increased an additional 1 to 2 tablets, resulting in a total daily dose of 5 to 6 tablets (500–600 mg/day of nefazodone). If intolerable side effects occurred, the dose could be reduced at any time (to a minimum of 100 mg/day).

Study Observations

The HAM-D-17 was used to establish eligibility and to assess therapeutic effect.[27] Additional measures of efficacy were the Clinical Global Impressions (CGI) Severity and Improvement scales,[27] the Montgomery-Asberg Depression Rating Scale (MADRS),[28] and the HAM-D depressed mood item (item 1) and retardation (items 1, 7, 8, 14), anxiety (items 10, 11, 12, 13, 15, 17), and sleep disturbance (items 4, 5, 6) factors.[27] Each patient was rated by the same person whenever possible to ensure consistency of patient evaluations. With the exception of the MADRS, which was scored only at the beginning and end of the trial, assessments were made at the end of the baseline evaluation, at the end of each study week, and at the end of the study or at the time a patient discontinued.

Three criteria were used to define "responders": a CGI-Improvement rating of at least much improved, a $\geq 50\%$ decrease from baseline in the HAM-D-17, or a HAM-D-17 score ≤ 10.

All patients were monitored for safety. Vital signs, which included temperature, weight, and supine and standing blood pressures and pulse rates, were obtained at all visits. Routine blood laboratory tests and standard 12-lead electrocardiograms were obtained at baseline, at week 4, and at the end of the study. Whenever blood was collected, additional amounts were obtained for plasma assays

of nefazodone and its metabolites (hydroxynefazodone, triazole-dione metabolite, *m*-chlorophenylpiperazine). These data will be presented elsewhere.

Statistical Methods

A 2-way analysis of variance (ANOVA) model that considered treatment, study center, and treatment-by-study-center interaction effects tested for baseline comparability and differences between treatments for the change from baseline scores. If baseline differences were significant ($p \leq .10$), adjustments for baseline differences were made using analysis of covariance with baseline level as a covariate. If the treatment-by-study-center interaction was not significant ($p > .10$) at week 6, the interaction term was dropped from the model. Computations were performed using the General Linear Model Procedure (PROC GLM) of SAS Version 6.08 (SAS Institute. Cary, N.C.). Treatment group means reported here were from the least-square means section of that analysis. To account for any missing data from a skipped visit, data from the most recent previous observation for that patient were carried forward. Categorical data were analyzed using the Cochran-Mantel-Haenszel statistic, stratifying by study center. Analyses (2-tailed) were performed for each study week and were considered significant if the p value was $\leq .05$. All patients who were randomized to treatment, who received a dose of study medication, and who had an efficacy evaluation during treatment were included in these analyses (the intent-to-treat data set).

RESULTS

Patient Description

Baseline data were obtained for all 120 patients enrolled in this study. The placebo (N = 59) and nefazodone (N = 61) groups were comparable with respect to demographic characteristics (Table 1). The psychiatric history of the patients is also included in Table 1. More than 80% of the patients in each treatment group were diagnosed with melancholia (and more than 80% in each group had CGI-Severity ratings of "marked" or worse).

In the first week of treatment, the mean modal daily dose of nefazodone was 366 mg and that of placebo was 3.7 tablets. By the end of the second week, the mean modal dose for nefazodone was 491 mg/day and for placebo was 4.8 tablets. During the last week of treatment, the mean modal daily dose of placebo was 5.1 tablets and that of nefazodone was 503 mg.

The majority of the patients (97%) in both treatment groups received concomitant CNS medications sometime during the trial. Benzodiazepines were used by 68% of the patients in the placebo group and 52% of the patients in the nefazodone group in the first week of the trial, but use diminished with time, such that 38% of the placebo patients and 16% of the nefazodone patients remaining at week 6 received a benzodiazepine. Overall, 73% of the patients in the placebo group and 66% of the patients in the nefazodone group used a benzodiazepine at some time during the trial. The benzodiazepines used most frequently were oxazepam, temazepam, and lorazepam. Clonazepam, triazolam, and alprazolam were rarely used. Nonsteroidal anti-inflammatory agents (NSAIDs), analgesics, and antipyretics were used intermittently. NSAIDs were used by 56% of the placebo patients and 46% of the nefazodone patients, while analgesics and antipyretics were used by 78% of the placebo patients and 72% of the nefazodone patients. Chloral hydrate was used by 7% of the patients in the placebo group and by 5% of the patients in the nefazodone group. Miscellaneous anxiolytics, sedatives, and hypnotics (e.g., hydroxyzine pamoate, hydroxyzine hydrochloride) were used by 7% of the placebo patients and by 3% of the nefazodone patients.

Table 1. Baseline Demographic Characteristics and Psychiatric History: Nefazodone vs. Placebo in Patients Hospitalized for Depression

Characteristic	Placebo (N = 59)	Nefazodone (N = 61)
Age, y (mean ± SE)	39.5 ± 1.6	37.2 ± 1.5
Sex, N (%)		
Female	37 (63%)	37 (61%)
Male	22 (37%)	24 (39%)
Race, N (%)		
White	48 (81%)	53 (87%)
Black	6 (10%)	5 (8%)
Hispanic	4 (7%)	3 (5%)
Other	1 (2%)	0 (0%)
Melancholia, N (%)	48 (81%)	54 (89%)
Recurrent episode, N (%)	30 (51%)	43 (70%)
Number of prior depressive episodes, mean ± SE	2.3 ± 0.5	1.6 ± 0.2
Age at onset of first depressive episode, y		
Mean	31.8	30.2
Range	12–74	11–71
SE	1.6	1.5
Previous antidepressant, N (%)	46 (78%)	40 (66%)
Duration of current episode, N (%)		
< 3 mo	7 (12%)	11 (18%)
3–5 mo	21 (36%)	20 (33%)
6–11 mo	10 (17%)	9 (15%)
> 12 mo	21 (35%)	21 (34%)

Efficacy

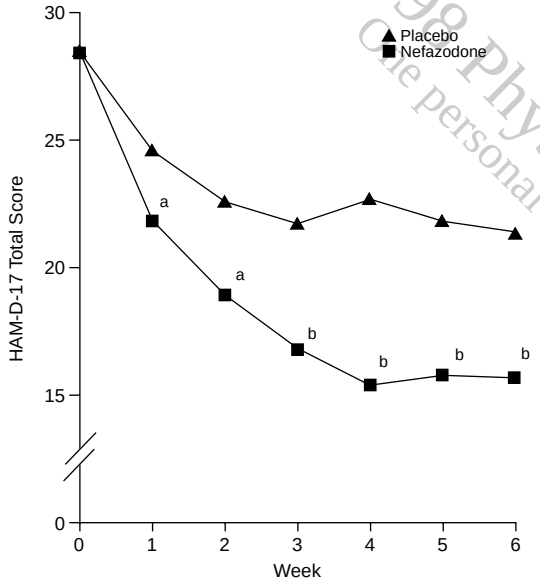
The intent-to-treat data set comprised 59 patients in the placebo group and 58 patients in the nefazodone group. Table 2 presents the mean baseline scores and changes from baseline at the end of treatment for the HAM-D-17, MADRS, and CGI. Baseline scores were comparable between the 2 treatment groups. At the end of treatment, nefazodone resulted in significant improvement compared with placebo on all measures. Figure 1 illustrates the reductions in the HAM-D-17 total score over time in both

Table 2. Summary of Efficacy Results at Endpoint: Nefazodone vs. Placebo in Patients Hospitalized for Depression*

	Placebo (N = 59)		Nefazodone (N = 58)	
Assessment	Baseline	Change at End of Treatment	Baseline	Change at End of Treatment
HAM-D-17 score, mean ± SE				
Total	27.9 ± 0.5	–7.7 ± 1.1	27.5 ± 0.5	–12.2 ± 1.2[b]
Depressed mood (item 1)	3.3 ± 0.1	–0.8 ± 0.2	3.2 ± 0.1	–1.4 ± 0.2[b]
Retardation factor	9.8 ± 0.2	–2.8 ± 0.4	9.4 ± 0.2	–4.3 ± 0.4[b]
Anxiety factor	8.5 ± 0.2	–1.9 ± 0.4	8.5 ± 0.2	–3.3 ± 0.4[b]
Sleep disturbance factor	4.3 ± 0.2	–1.1 ± 0.3	4.4 ± 0.2	–2.3 ± 0.3[b]
MADRS total,[c] mean ± SE	35.1 ± 0.6	–8.1 ± 1.5	35.6 ± 0.7	–17.2 ± 1.6[b]
CGI score				
Severity, mean ± SE	4.9 ± 0.1	–0.9 ± 0.2	5.0 ± 0.1	–1.6 ± 0.2[b]
Improvement, % responders (N)	n/a	29% (17/59)	n/a	50%[a] (29/58)

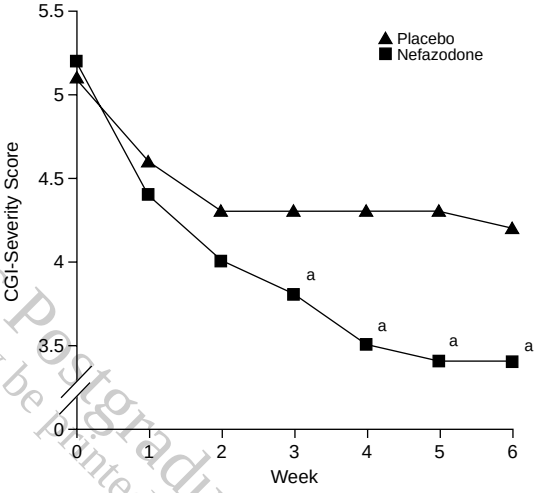
*Abbreviations: CGI = Clinical Global Impressions scale, HAM-D-17 = Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, n/a = not applicable.
[a].01 < p ≤ .05, [b]p ≤ .01, ANOVA (HAM-D-17, CGI-Severity, MADRS), Cochran-Mantel-Haenszel (CGI-Improvement), comparison with placebo, intent-to-treat data set, last observation carried forward (LOCF).
[c]Placebo N = 57, nefazodone N = 52.

Figure 1. Mean Change in HAM-D-17 Total Score by Weekly Visit



[a]p ≤ .05, [b]p < .01 based on ANOVA of mean change from baseline scores; LOCF, intent-to-treat data set.

Figure 2. Mean Change in CGI-Severity Score by Weekly Visit



[a]p < .02 based on ANOVA of mean change from baseline scores; LOCF, intent-to-treat data set.

treatment groups. Significant differences were seen at all treatment weeks, beginning as early as the end of the first week. Similarly, nefazodone's efficacy appeared to emerge as early as week 1 based on reduction in CGI-Severity mean scores, with statistical differences between treatment groups seen by week 3 (p = .012) and continuing through the end of treatment (Figure 2).

Table 3 summarizes response rates by treatment week. By the second week of treatment, significantly more nefazodone-treated patients than placebo-treated patients had responded by 2 of the 3 criteria (p = .036 for ≥ 50% HAM-D-17 decrease, and p = .001 for HAM-D-17 ≤ 10), and differences were significant (p = .009) by the end of week 3 by the third response criterion (CGI-Improvement). At the end of treatment, 50% of the nefazodone-treated compared with 29% of the placebo-treated patients were responders based on a ≥ 50% reduction in their HAM-D-17 total score (p = .017) or a CGI-Improvement score of much or very much improved (p = .021). Some 36% of the nefazodone group, compared with 14% of the placebo group, had a HAM-D-17 score equal to or less than 10 at the end of treatment (p = .004). Conversely, significantly fewer nefazodone-treated patients (18/58 or 31%) exhibited a HAM-D-17 ≥ 20 than did placebo-treated patients (33/59 or 56%) at the end of treatment (p ≤ .01).

Nefazodone-treated patients had significant improvements compared with placebo-treated patients by week 3 (and thereafter) on the HAM-D retardation (p = .024) and

Table 3. Number of Patients (%) Responding by Treatment Week: Nefazodone vs. Placebo in Patients Hospitalized for Depression

	CGI-Improvement Score of Much or Very Much Improved				≥ 50% Decrease on the HAM-D-17				HAM-D-17 Score ≤ 10			
	Placebo (N = 59)		Nefazodone (N = 58)		Placebo (N = 59)		Nefazodone (N = 58)		Placebo (N = 59)		Nefazodone (N = 58)	
Week	N	%	N	%	N	%	N	%	N	%	N	%
1	7	12	10	17	4	7	8	14	0	0	2	3
2	12	20	19	33	7	12	16	28[a]	1	2	12	21[b]
3	12	20	25	43[b]	5	8	23	40[b]	2	3	14	24[b]
4	11	19	28	48[b]	8	14	27	47[b]	2	3	19	33[b]
5	15	25	26	45[a]	12	20	26	45[b]	6	10	17	29[b]
6	17	29	29	50[a]	17	29	29	50[a]	8	14	21	36[b]

[a].01 < p ≤ .05, [b]p ≤ .01; Cochran-Mantel-Haenszel comparison with placebo, intent-to-treat data set, LOCF.

Table 4. Treatment Response in Subsets of Inpatients With Major Depression With or Without Dysthymia: Nefazodone vs. Placebo in Patients Hospitalized for Depression

	With Dysthymia				Without Dysthymia			
	Placebo (N = 23)		Nefazodone (N = 22)		Placebo (N = 32)		Nefazodone (N = 34)	
Assessment	N	%	N	%	N	%	N	%
Responders at endpoint								
CGI-Improvement	4	17	12	55[b]	11	34	16	47
HAM-D ≥ 50% change	3	13	11	50[b]	12	38	17	50
HAM-D ≤ 10	1	4	7	32[a]	6	19	14	41[a]
HAM-D-17 total score	Mean	SE	Mean	SE	Mean	SE	Mean	SE
Baseline	27.9	0.9	28.3	1.0	28.0	0.6	27.2	0.6
Change at endpoint	–4.4	2.0	–12.1[b]	2.2	–8.2	1.5	–13.0[a]	1.5

[a].01 < p ≤ .05, [b]p ≤ .01; ANOVA (HAM-D-17 total), Cochran-Mantel-Haenszel (percentage of responders), comparison with placebo, intent-to-treat data set, LOCF.

anxiety factors (p = .003) and on the depressed mood item (p = .045). At the end of treatment, the differences on all 3 of these measures were highly significant: retardation (p = .007), anxiety (p = .009), and depressed mood (p = .003). The HAM-D sleep disturbance factor was significantly improved in the nefazodone group compared with placebo at the end of the first week of treatment (p = .012) through the end of treatment (p = .003). The MADRS also showed significantly greater improvement from baseline to end of treatment (p = .001) for the nefazodone group (–17.2) than for the placebo group (–8.1).

Twenty-three patients in the placebo group and 22 patients in the nefazodone group were diagnosed as dysthymic as well as having major depression, i.e., they met the diagnostic criteria for "double depression." Endpoint results for this subset of patients are presented in Table 4. Significant improvement was observed for nefazodone treatment compared with placebo treatment by each of the 3 responder definitions, with statistically significant treatment differences seen from the end of week 2 through the end of the trial. For example, 55% of the nefazodone-treated patients with double depression had CGI-Improvement ratings of much or very much improved at endpoint compared with 17% of the placebo-treated patients (p = .011), and at the end of 3 weeks, the percentages of responders in the nefazodone and placebo treatment groups were 50% and 17%, respectively (p = .032). In addition, there was a difference in mean HAM-D-17 total scores of 7.7 points at endpoint (change of –12.1 for nefazodone vs. –4.4 for placebo, p = .002).

Fifty-one percent of the patients in the nefazodone group completed the study compared with 44% in the placebo group (Table 5). The most frequent reason that patients discontinued from the study was the clinician's judgment of lack of efficacy: 37% in the placebo group and 25% in the nefazodone group. A Kaplan-Meier survival analysis (Figure 3) showed that nefazodone treatment resulted in a lower rate of discontinuation for lack of efficacy, with the differences between treatments approaching statistical significance (p = .061).

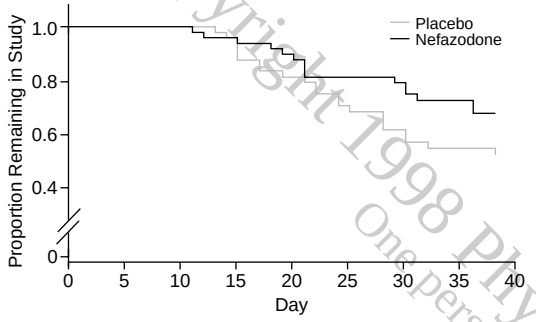
Safety

Most of the patients in each treatment group reported 1 or more adverse events at some time during the study (95% for nefazodone, 85% for placebo). Table 6 summarizes the treatment-emergent adverse events (i.e., those

Table 5. Study Completion Rates and Reasons for Discontinuation: Nefazodone vs. Placebo in Patients Hospitalized for Depression

	Placebo (N = 59)		Nefazodone (N = 61)	
Status	N	%	N	%
Completed study	26	44	31	51
Discontinued	33	56	30	49
Lack of efficacy	22	37	15	25
Adverse event	6	10	8	13
Patient withdrew consent	4	7	2	3
Lost to follow-up	0	0	5	8
Patient unreliable	1	2	0	0

Figure 3. Time to Discontinuation for Lack of Efficacy



that were first reported or worsened after initiation of double-blind treatment) that were reported by 10% or more of the patients in the nefazodone treatment group. Of these events, those that occurred at more than twice the rate in the nefazodone group compared with placebo were somnolence, dry mouth, dyspepsia, asthenia, blurred vision, abnormal vision, and abnormal dreams. Comparable numbers of patients withdrew from the trial because of adverse events in the nefazodone (N = 8) and placebo (N = 6) groups.

DISCUSSION

Studies have shown that severely depressed patients often are not as responsive to pharmacotherapy as moderately depressed patients.[29] Nonetheless, the response to nefazodone in comparison with placebo in this inpatient study is similar to that observed in placebo-controlled outpatient studies.[19–22] Even though 82% of the patients in this study were severely depressed (i.e., HAM-D-17 total score ≥ 25 at baseline[30]), significantly more nefazodone-treated than placebo-treated patients were responders to treatment by each of the 3 responder definitions, and the reductions in the mean HAM-D-17, CGI-Severity, and MADRS scores were significantly greater for the nefazodone group than for the placebo group. At the end of the study, 50% of the patients in the nefazodone group had responded to treatment as judged by either a ≥ 50% reduction in their HAM-D-17 score or a CGI-Improvement score of 1 or 2, and more than twice as many patients in the nefazodone group than in the placebo group had a reduction of their HAM-D-17 total score to 10 or less. These results provide clear evidence of the utility of nefazodone for the treatment of marked to severe depression in patients requiring hospitalization.

Table 6. Adverse Events Reported by ≥ 10% of the Nefazodone-Treated Patients: Nefazodone vs. Placebo in Patients Hospitalized for Depression

	Placebo (N = 59)		Nefazodone (N = 61)	
Adverse Event	N	%	N	%
Somnolence	10	17	29	48[b]
Headache	27	46	25	41
Nausea	14	24	22	36
Dizziness	11	19	19	31
Dry mouth	5	8	15	25[a]
Dyspepsia	5	8	11	18
Asthenia	3	5	10	16[a]
Constipation	4	7	8	13
Blurred vision	2	3	8	13
Diarrhea	8	14	7	11
Abnormal vision	3	5	7	11
Insomnia	5	8	7	11
Pharyngitis	5	8	7	11
Abnormal dreams	3	5	6	10

[a]$p \le .05$, [b]$p \le .01$ compared with placebo; Pearson chi-square test.

Response to nefazodone treatment was rapid, as evidenced by significant differences from placebo in the mean HAM-D-17 total score as early as the end of week 1. This rapid response may reflect the aggressive escalation of the dose in the first week or two of the trial, a practice not uncommon in hospitalized patients who are generally more severely ill and tend to tolerate higher doses of medication. The mean daily dose of 491 mg at the end of week 2 was essentially the same as that at the end of the trial (503 mg).

It is particularly encouraging to observe the response to nefazodone in patients with a chronic antedating diagnosis of dysthymia in addition to major depression, since patients with chronic depression are often considered to be resistant to treatment with antidepressant drugs.[31,32] As is typical of patients with double depression,[32] the response rate for placebo-treated patients in this subset was low (at the end of the trial, ranging from 4% to 17% depending on the response criterion); however, the response to nefazodone was marked (32% to 55% at end of treatment) and significantly different from placebo as early as week 2. Furthermore, the change from baseline to endpoint in HAM-D-17 scores for the nefazodone group (–12.1) was significantly greater than for the placebo group (–4.4). In total, these findings indicate that patients with double depression respond to nefazodone treatment and do so in a robust manner. This is in accord with Howland's suggestion that serotonergic antidepressants may have particular utility in managing patients with chronic depression.[33] Treatment differentiation in the nondysthymic subset was limited by the higher placebo re-

sponse rate and the small sample size associated with the subgroup analysis; however, even in this subset, statistically significant treatment differences were seen based on the HAM-D-17 ≤ 10 responder criterion and on HAM-D-17 mean changes.

Numerous trials in depression have demonstrated that patients with melancholia are more responsive to pharmacotherapy than patients without melancholia.[34] The majority of the patients in this study had melancholia (89% for nefazodone, 81% for placebo); however, there were too few patients in the non-melancholic group (11 for placebo, 7 for nefazodone) to make any comparisons.

The adverse events reported in this trial are consistent with those reported previously for nefazodone[35] as well as with nefazodone's pharmacology, the patient population and treatment setting, and the dosing regimen employed. Discontinuation rates due to adverse experiences were similar between the 2 treatment groups (6 patients in the placebo group vs. 8 patients in the nefazodone group). No significant safety issues were noted in either group. The relatively high mean nefazodone dose achieved and the speed of titration may have led to a somewhat higher incidence than normally seen for some of the most frequently reported side effects (e.g., somnolence, nausea, and dizziness). In particular, somnolence, the most frequently occurring side effect in the nefazodone group, was reported by 48% of the patients, compared with 17% in the placebo group. However, daytime somnolence did not appear to affect nighttime sleep. In fact, sleep improved for the nefazodone-treated patients, as evidenced by significant decreases in the mean HAM-D sleep disturbance factor scores from the first week through the end of the trial. Among the 29 nefazodone patients who reported somnolence, half did so during their first 5 days of treatment, as might be expected based on the aggressive dose titration. Most patients either developed a tolerance for this side effect and/or had their dosing regimen changed so that a larger portion of the daily dose was administered at bedtime or had their dose reduced. As the trial progressed, patients treated with nefazodone also received fewer concomitant benzodiazepines than did placebo-treated patients. This reduction is consistent with the significant relief of anxiety symptoms seen in the nefazodone-treated patients as well as with the improvements seen in sleep for these patients compared with those treated with placebo.

In conclusion, this study demonstrates the clear superiority of nefazodone compared with placebo in the treatment of marked to severe major depression in patients requiring hospitalization. Nefazodone is one of only a few of the newer antidepressants to have been demonstrated to be efficacious in inpatients. In these patients, the clinical benefit of nefazodone was evident as early as the first week of treatment as judged by several measures of efficacy, with significant differences from placebo sustained throughout the trial.

Drug names: alprazolam (Xanax), chloral hydrate (Noctec), clonazepam (Klonopin), fluoxetine (Prozac), fluvoxamine (Luvox), hydroxyzine (Vistaril), imipramine (Tofranil and others), lorazepam (Ativan and others), mirtazapine (Remeron), nefazodone (Serzone), oxazepam (Serax and others), paroxetine (Paxil), sertraline (Zoloft), temazepam (Restoril and others), triazolam (Halcion), venlafaxine (Effexor).

REFERENCES

1. Klerman GL, Weissman MM, Frank E, et al. Evaluating drug treatments of depressive disorders. In: Prien RF, Robinson DS, eds. Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines. New York, NY: Raven Press; 1994:281–325
2. Mazure CM, Nelson JC, Jatlow PI. Predictors of hospital outcome without antidepressants in major depression. Psychiatry Res 1990;33:51–58
3. Edwards JG. Ethics of placebo-controlled trials in depression [editorial]. Hum Psychopharmacol 1989;4:235–236
4. Edwards JG. Ethics of placebo-controlled trials in depression: a reply to a reply. Hum Psychopharmacol 1989;5:374–375
5. Lasagna L. Decision processes in establishing the efficacy and safety of psychotropic agents. In: Prien RF, Robinson DS, eds. Clinical Evaluation of Psychotropic Drugs: Principles and Guidelines. New York, NY: Raven Press; 1994:13–28
6. Manna V, Martucci N, Agnoli A. Double-blind controlled study on the clinical efficacy and safety of fluoxetine vs clomipramine in the treatment of major depressive disorders. Int Clin Psychopharmacol 1989;4(suppl 1): 81–88
7. de Jonghe F, Ravelli DP, Tuynman-Qua H. A randomized, double-blind study of fluoxetine and maprotiline in the treatment of major depression. Pharmacopsychiatry 1991;24:62–67
8. Beasley CM, Holman SL, Potvin JH. Fluoxetine compared with imipramine in the treatment of inpatient depression. Ann Clin Psychiatry 1993;5: 199–208
9. Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143
10. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
11. Feighner JP, Boyer WF, Meredith CH, et al. A placebo-controlled inpatient comparison of fluvoxamine maleate and imipramine. Int Clin Psychopharmacol 1989;4:239–244
12. Guelfi JD, White C, Magni G. A randomized double-blind comparison of venlafaxine and placebo in inpatients with major depression and melancholia [abstract]. Clin Neuropharmacol 1992;15(suppl 1, pt B):323B
13. Feighner JP. The role of venlafaxine in rational antidepressant therapy. J Clin Psychiatry 1994;55(9, suppl A):62–70
14. Khan MC. A randomized, double-blind, placebo-controlled, 5-weeks study of ORG-3770 (mirtazapine) in major depression. Hum Psychopharmacol 1995;10(suppl 2):S119–S124
15. Edwards JG, Goldie A. Placebo-controlled trial of paroxetine in depressive illness. Hum Psychopharmacol 1993;8:203–209
16. Eison A, Eison M, Torrente J, et al. Nefazodone: preclinical pharmacology of a new antidepressant. Psychopharmacol Bull 1990;26:311–315
17. Taylor DP, Carter RB, Eison AS, et al. Pharmacology and neurochemistry of nefazodone, a novel antidepressant drug. J Clin Psychiatry 1995;56 (suppl 6):3–11
18. Feighner JP, Pambakian R, Fowler RC, et al. A comparison of nefazodone, imipramine, and placebo in patients with moderate to severe depression. Psychopharmacol Bull 1989;25:219–221
19. Rickels K, Schweizer E, Clary C, et al. Nefazodone and imipramine in major depression: a placebo-controlled trial. Br J Psychiatry 1994;164: 802–805
20. Fontaine R, Ontiveros A, Elie R, et al. A double-blind comparison of nefazodone, imipramine, and placebo in major depression. J Clin Psychiatry 1994;55:234–241
21. Cohn CK, Robinson DS, Roberts DL, et al. Responders to antidepressant drug treatment: a study comparing nefazodone, imipramine, and placebo in patients with major depression. J Clin Psychiatry 1996;57(suppl 2): 15–18
22. Mendels J, Reimherr F, Marcus RN, et al. A double-blind, placebo-con-

trolled trial of two dose ranges of nefazodone in the treatment of depressed outpatients. J Clin Psychiatry 1995;56(suppl 6):30–36
23. Baldwin DS, Hawley CJ, Abed RT, et al. A multicenter double-blind comparison of nefazodone and paroxetine in the treatment of outpatients with moderate-to-severe depression. J Clin Psychiatry 1996;57(suppl 2):46–52
24. Feiger A, Kiev A, Shrivastava RK, et al. Nefazodone versus sertraline in outpatients with major depression: focus on efficacy, tolerability, and effects on sexual function and satisfaction. J Clin Psychiatry 1996;57(suppl 2):53–62
25. Rioux P, Kibleur Y, Frachon O, et al. A double-blind comparison of nefazodone and fluoxetine in depressed patients. In: New Research Program and Abstracts of the 149th Annual Meeting of the American Psychiatric Association; May 7, 1996; New York, NY. Abstract NR359:164
26. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1994
27. Guy W. ECDEU Assessment Manual for Psychopharmacology, revised. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:179–222
28. Montgomery SA, Asberg M. A new depression scale designed to be sensitive to change. Br J Psychiatry 1979;134:382–389
29. Kocsis JH, Croughan JL, Katz MM, et al. Response to treatment with antidepressants of patients with severe or moderate nonpsychotic depression and of patients with psychotic depression. Am J Psychiatry 1990;147: 621–624
30. Hirschfeld RA. Diagnosing severely depressed patients in clinical trials and in clinical settings. pp 554–556. In: Controversies in the Diagnosis and Treatment of Severe Depression [ACADEMIC HIGHLIGHTS]. J Clin Psychiatry 1996;57:554–561
31. Coryell W, Endicott J, Keller MB. Outcome of patients with chronic affective disorder: a five-year follow-up. Am J Psychiatry 1990;147: 1627–1633
32. Keller MB, Harrison W, Fawcett JA, et al. Mood disorders. Psychopharmacol Bull 1995;31(2):205–212
33. Howland RH. Chronic depression. Hosp Community Psychiatry 1993;44: 633–639
34. Karasu TB, chair, for the Work Group on Major Depressive Disorder. Practice Guideline for Major Depressive Disorder in Adults. Am J Psychiatry 1993;150(suppl 4):1–26
35. Preskorn SH. Comparison of the tolerability of bupropion, fluoxetine, imipramine, nefazodone, paroxetine, sertraline, and venlafaxine. J Clin Psychiatry 1995;56(suppl 6):12–21