A double-blind comparison of nefazodone and fluoxetine in the treatment of depressed outpatients

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Summary

Background

Nefazodone is a recently released antidepressant that has shown similar efficacy in clinical trials when compared to tricyclic antidepressants and to some serotonin selective reuptake inhibitors (SSRI'S). It has also demonstrated to be better tolerated than tricyclics and with an equivalent tolerance with respect to SSRI'S. However comparisons with fluoxetine have not been reported. Being fluoxetine a worldwide highly prescribed antidepressant, a comparative trial of both drugs would be of interest.

Method

A total of 74 outpatients with a major depressive episode (DSM-III-R) entered into an 8-week trial to compare the efficacy and tolerance of nefazodone and fluoxetine in a double-blind, randomized parallel group design. Evaluations were performed at weekly intervals using the Hamilton scales for depression and anxiety (HAM-D and HAM-A), as well as the Clinical Global Impression (CGI) and Patient Global Assessment (PGA) scales to compare efficacy. Tolerance and safety were compared using reports of adverse events. Results analyses were performed both on the Last Observation Carried Forward (LOCF) and visitwise data sets, with an analysis of Variance (ANOVA) model to test for differences between treatments from baseline and within the different study weeks.

Results

Thirty seven patients received fluoxetine (mean dose 24.0 mgs/day), and 37 received nefazodone (mean dose 400.0 mgs/day). However one patient in the nefazodone group did not have at least one eficacy evaluation during treatment and was excluded from the analysis. Demographic and clinical characteristics did not differ between the groups. At the end of week 8, the 17-item HAM-D total score (LOCF data set) mean change was −12.4 for fluoxetine and −12.3 for nefazodone, showing a comparable antidepressant response. No differences between groups were also observed when comparing several individual depressive items, as well as the remaining scales. Anxiety symptoms were reduced comparatively according to the mean change from baseline in the total HAM-A scores (−10.0 in both groups). In general both drugs were well tolerated generating moderate side-effects tha did not interfere with treatment outcome. Safety assessment revealed no evidence that nefazodone administration resultad in any medically serious adverse events or in organic toxicity based on physical examination findings and significant abnormal laboratory values.

Conclusions

The results of the study indicate that both nefazodone and fluoxetine are of equivalent efficacy for treating moderate to severe major depression. Nefazodone was found to be safe and well tolerated, without any important differences with respect to fluoxetine. Further studies are needed to characterize the efficacy of nefazodone in other forms of depression and also to evaluate its efficacy and effects over longer periods of treatment.

Key words: Nefazodone, fluoxetine, antidepressant treatment, efficacy and safety comparisons.

Resumen

Antecedentes

La nefazodona es un antidepresivo desarrollado recientemente, que ha demostrado poseer una eficacia similar a la de los antidepresivos tricíclicos y a la de algunos de los inhibidores selectivos de la recaptura de la serotonina (ISRS). También ha demostrado tener mayor tolerancia que los tricíclicos y similar a la de los de los ISRS. Sin embargo, hasta este momento no han aparecido reportes en los que se le compare específicamente con la fluoxetina. Debido a que este último antidepresivo se utiliza de manera muy extendida

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alrededor del mundo, su comparación con la nefazodona por medio de un estudio clínico controlado, es de gran interés.

Metodología

Un total de 74 pacientes de la consulta externa, diagnosticados como portadores de un episodio depresivo mayor de acuerdo a los criterios diagnósticos del DSM-III-R, fue reclutado para participar en un ensayo clínico con el objetivo de comparar la eficacia y la tolerancia entre la nefazodona y la fluoxetina. El estudio se llevó a cabo por medio de un procedimiento doble-ciego con asignación aleatoria de medicamento en dos grupos paralelos. Las evaluaciones se efectuaron con una periodicidad semanal, en las cuales se hizo una valoración clínica global de cada paciente, que incluía la aplicación de las escalas de Hamilton para depresión (EDH) y ansiedad (EAH), la Escala de Impresión Clínica Global (ICG) y la de Evaluación Global del Paciente (EGP) para determinar la eficacia del tratamiento. La tolerancia y seguridad de los tratamientos se comparó con la aplicación de escalas pertinentes para ello. El análisis de los resultados se efectuó utilizando dos procedimientos: el procedimiento de acarreo de la última observación (AUO) y el de los datos agrupados de cada visita. Los datos se analizaron por medio de un análisis de varianza (ANOVA) para medidas repetidas, con la finalidad de buscar diferencias entre los dos tratamientos, partiendo del momento del inicio (periodo basal) y a lo largo de las semanas consecutivas de tratamiento.

Resultados

Treinta y siete pacientes recibieron fluoxetina (dosis diaria promedio 24 mgs) y 37 recibieron nefazodona (dosis diaria promedio 400 mgs), sin embargo un paciente del grupo de la nefazodona no alcanzó a tener por lo menos una evaluación de eficacia a lo largo del estudio, por lo que se excluyó del análisis. Las características clínicas y demográficas resultaron ser similares entre los dos grupos. Al final de la semana 8 de tratamiento la calificación total de la EDH (versión de 17 reactivos) se redujo en promedio −12.4 puntos en el grupo que recibió fluoxetina y en −12.3 en el grupo que recibió nefazodona, demostrando que la respuesta antidepresiva es similar en los 2 fármacos. Tampoco se encontraron diferencias entre los grupos cuando los reactivos de la escala se analizaron en forma individual, ni tampoco cuando se analizaron las puntuaciones del resto de las escalas de depresión. La sintomatología ansiosa también se redujo en forma comparativa en los 2 grupos, de acuerdo con los cambios cuantificados en la puntuación total de la EAH (−10.0 en ambos grupos). En términos generales ambos fármacos fueron bien tolerados, generando efectos colaterales moderados que no interfirieron en ningún momento con el efecto antidepresivo. Las evaluaciones de seguridad no encontraron ningún problema médico adverso severo en los pacientes que tomaron nefazodona. Tampoco se encontraron anormalidades importantes en las evaluaciones físicas de los pacientes o en los resultados de los análisis de laboratorio efectuados a lo largo del estudio.

Conclusiones

Los resultados del estudio indican que tanto la nefazodona como la fluoxetina tienen una equivalencia similar en cuanto a su eficacia para el tratamiento de la depresión de moderada a severa. Se comprobó que la nefazodona es un antidepresivo seguro y bien tolerado cuando se administra a dosis terapéuticas, sin que existiera ninguna diferencia en estos aspectos en comparación con la fluoxetina. Se requieren estudios más específicos para determinar si la nefazodona es más eficaz en algunos subtipos específicos de depresión y para evaluar los parámetros de eficacia y seguridad en periodos más prolongados de tratamiento.

Palabras clave: Nefazodona, fluoxetina, tratamiento antidepresivo, eficacia, tolerancia.

Depression is a common disorder in the general population that often is underdiagnosed and undertreated. However the high prevalence rate, and the increased morbidity associated with this disorder is now being appreciated (16). The tricyclic antidepressant drugs have been for many years the standard first-line treatment for depression, but although highly effective, they present some problems with respect to safety and side effects that frequently affect the patient's compliance. Recently the new antidepressant drugs like fluoxetine, paroxetine and other serotonin selectiva reuptake inhibitors (SSRI'S), as well as other compounds such as bupropion, venlafaxine or nefazodone, have contributed to solve these problems by offering compounds that are similarly effective as tricyclic drugs, yet at the same time have better tolerability and safety profile, so they may add substantial benefits in treating these patients, as long as it is proved that they are as effective as the currently available antidepressants. These drugs have added substantial benefits in treating these patients and at the same time have expanded the treatment options for those who present difflculties in responding to some but not all medications.

Nefazodone, a phenylpiperazine compound with antidepressant activity, has shown similar efficacy in several clinical trials when compared to the tricyclic antidepressants imipramine (7,15) and amitriptyline (2), and also when compared to the SSRI'S paroxetine and sertraline, demonstrating a similar response (4,6).

Nefazodone has also been used for the treatment of other clinical disorders, such as premenstrual syndrome (8). Its antidepressant activity derives from two main mechanisms of action: a) a 5-HT2 receptor antagonism and b) a moderate 5-HT reuptake inhibition; these actions enhance serotoninergic neurotransmission, which is postulated to be a chemical pathway for restoring affective dysregulation (3). In comparison to tricyclics, nefazodone is equally effective, but generally better tolerated as reflected by a lower attrition rate due to adversa events and a more benign profile of side-effects. These resuits were expected as the drugs comparad have different neurochemical profiles, nefazodone resembling more the effects of trazodone to which it is structurally relatad. However nefazodone may have a more favorable side-effects profile than trazodone because some of. the negativa effects of serotonin uptake inhibition, as for example nausea or gastrointestinal cramps, may be diminíshed by nefazodone's potent 5-HT2 antagonist activity (5). Comparad to the SSRI's with respect to side-effects, nefazodone has no sustantial differences in most measured parameters, with the exception of sexual dysfunction, which in one study was significantly less when compared to sertraline (6). In addition the compound has only a slight alpha I adrenergic activity, virtually no cardiotoxicity and no anticholinergic or histaminergic activity (5). Its main treatment emergent side-effects include somnolence, dizziness, asthenia, dry mouth, constipation, headache and blurred vision. After oral administration nefazodone is rapidly absorbed with a bioavaliability of about 20 %. It bounds highly to proteins and, depending on dose, elimination half-

life ranges from 2 to 4 hours. Metabolism of the general compound generates two active metabolites: OH-nefazodone end m-chlorophenylpiperazine (m-cpp), both also having short half-lives. A third metabolite, triazolo-dione, has also been identified, but its pharmacological profile has not yet been well characterized (17).

Nefazodone is en effective new antidepressant similar to tricyclics and other antidepressants, but with a low side-effect profile which is beneficial for many patients and also for the long-term treatment of depression. However, therapeutic benefits relative to other antidepressant drugs, such as fluoxetine, have not yet been compared. As fluoxetine is a widely prescribed drug and also better tolerated than tricyclics, comparison to nefazodone is highly needed. The current study was designed to assess antidepressant eficacy and tolerability of nefazodone compared with fluoxetine in psychiatric outpatients suffering from major depression.

Method

The study was a two-center, randomized, double-blind, double-dummy parallel group comparison of the safety and efficacy of nefazodone and fluoxetine in the treatment of moderately to severely depressed outpatients. Each patient participated in a one-to-four week baseline evaluation phase designed to ensure that there was an adequate drug-free interval before the double-blind treatment phase, that all eligibility criteria were fulfilled and that all relevant baseline data were recorded. To qualify for inclusion in the trial, patients had to fulfill DSM-III-R criteria (1) for moderate to severe mejor depressive episode without psychotic features or bipolar disorder of the depressed type. Patients had to be 18 years of age or older and had to have a total score of 18 points or above on the first 17 items of the Hamilton Rating Scale for Depression (HAM-D) (10) at baseline. Female patients, if in fertile stage of life, had to use reliable contraceptive methods. Exclusion criteria included the presence of a concomitant organic mental disorder, psychoactive substance use disorder, schizophrenia or other psychotic disorder or any medical condition that contraindicated treatment with antidepressants; women who were pregnant or lactating aiso were exciuded from the study. Concomitant psychotropic medication was prohibited, except for the occasional use of benzodiazepines to treat severe anxiety or insomnia.

At the end of baseline, patients who qualified for the double-blind treatment phase were randomized to twice-daily dosing with either nefazodone or fluoxetine and received study medication orally for the next eight weeks. Patients were assessed at baseline, and weekly thereafter with a final evaluation at the end of week 8. The HAM-D, Hamilton Rating Scale for Anxiety (HAM-A) (11), Clinical Global Impression (CGI) and Patient Global Assessment (PGA) scales (9) were completed at every visit as clinical outcome measures. Safety was assessed using reports of adverse events including intercurrent illness, vital signs measurements, physical examinations, electrocardiogram (EKG) and clinical laboratory tests. All adverse events were evaluated by the investigators in terms of incidence, duration, severity and possible relationship to test medication; they were recorded in a case report form for adverse events. The initial daily dosage of medications was 200 mg for nefazodone end 20 mg for fluoxetine; nefazodone was increased after the first week to 400 mg. After 4 weeks of treatment in the absence of significant clinical improvement and in the absence of intolerable adverse events, the daily dosage could be increased to 500 mg of nefazodone and 40 mg of fluoxetine. Mean daily medication doses remained rather stable throughout the study, and at the end of week 8 of treatment, 400.0 mg nefazodone and 24.0 mg fluoxetine were administered. Nineteen (51 %) patients in the fluoxetine group and 14 (38%) in the nefazodone group required treatment with benzodiazepines for some time during the trial period. Participation in the study could be discontinued early for any of the following reasons: adverse event, administrative reason such as non compliance or discovery of a protocol violation, lack of eficacy, investigator's decision that continuation would not be in the patient's best interest or patient's decision not to continue.

The study was conducted in accordance with generally accepted standards for the protection of patient safety and welfare. It was approved by the institutional ethic committees of the participant centers and written informed consent was obtained before a patient entered the study. Any patient who did not complete the study was evaluated at the time of early discontinuation and had final assessment measures and the reason given for discontinuation recordad. The intent-to-treat (ITT) sample was defined as those patients who received a dose of the study medication and had an efficacy evaluation during treatment. Analyses of the ITT sample were performed on the Last Observation Carried Forward (LOCF) and visitwise data sets. The LOCF data set induded patients data recordad at a given visit or, if no observation was recorded at that visit, data were carried forward from the previous visit. The visitwise data set consisted of the actual observation at each visit for weeks 1 through 8.

The analyses of the HAM-D, CGI severity and HAM-A scores were done with an analysis of variance (ANOVA) model which considered treatment, study center and treatment by study center interaction effects. The ANOVA model was used to test for baseline comparability as well as differences between treatments for changes from baseline (12). Categorical data, such as CGI and PGA improvement scores, were analyzed within the framework of the generalized Cochran-Mantel-Haenszel procedure (CMH), stratifyng by study center. Both the two-way ANOVA and CMH models tested the differences between treatments averaged across study centers. Ninety-five percent confidence intervals on the treatment effect analyses were performed at each study week. The planned sample size of 80 patients had a power of 80% to detect an average difference of six points in the HAM-D 17 total score between the nefazodone and fluoxetine treatment groups. All probability testing was two-tailed with p

values rounded to two decimal places; p values less than or equal to .01 were regarded as significant, and values greater than .01 but less than or equal to .05 were regarded as indicative of a trend.

The baseline end weekly data that were evaluated by an ANOVA for the LOCF and visitwise data sets were: HAM-D's total score, anxiety factor, retardation factor, sleep disturbance factor, item 1 (depressed mood), CGI doctor's opinion of improvement and of severity, and HAM-A total score. If the treatment by study center interaction was nonsignificant ($p < .10$) at week 8, the interaction term was dropped from the model. When baseline differences were significant ($p \leq .10$), adjustment for baseline differences were made using Analysis of Covariance (ANCOVA) with baseline level as the covariate. A responder/nonresponder categorization was used to summarize the patient's and doctor's opinion of improvement at each visit. Patients were categorized es responders if they were rated "much improved" or "very much improved"; otherwise they were classified as nonresponders. The CMH procedure was used to test the hypothesis of an association between treatment and response averaged over study centers. All statistical computations were performed with SAS version 6.08, ANOVA and ANCOVA analyses were performed with the general linear model procedure. Categorical analyses were performed with the frequency procedure. All patients who were dispensed treatment were included in the safety evaluation, and findings of any potential significance were carefully reviewed for clinical importance by a physician from the supporting pharmaceutical institution's research and development group.

Results

A total of 74 patients from two recruitment centers were included in the study. Of these, 64 (86%) completed the acute phase and 10 (14%) discontinued early. However one patient in the nefazodone group did not have an efficacy evaluation during treatment and was therefore excluded, so the ITT sample comprised 37 patients in the fluoxetine group and 36 patients in the nefazodone group. The demographic and clinical characteristics of the subjects by treatment group are presented in table 1. Both groups were comparable with respect to age, sex, and marital status. The case records showed that 16 patients (22%) presented a major depressive episode of the melan-

TABLE 1
Demographic Characteristics and Psychiatric and Treatment History

Variable	*Fluoxetine N = 37*	*Nefazodone N = 37*	*Total N = 74*
Age (Y)			
Mean	39.9	41.5	40.7
Median	40	42	41
Range	20-75	19 - 69	19 - 75
S.E.	2.2	2.1	1.5
Sex, N (%)			
Men	9 (24)	8 (22)	17 (23)
Women	28 (76)	29 (78)	57 (77)
Primary Diagnosis, N (%)			
Major Depressive Disorder	37 (100)	37 (100)	74 (100)
Melancholia, N (%)			
Yes	7 (19)	9 (24)	16 (22)
No	30 (81)	26 (76)	58 (78)
Single/Recurrent, N (%)			
Single	20(54)	22 (59)	42 (57)
Recurrent	17 (46)	15 (41)	32 (43)
Number of Prior Depressive Episodes			
Mean	1.1	1.1	1.1
Median	0	0	0
Range	0-10	0-6	0-10
S.E.	0.3	0.3	0.2
Not Recorded	0	2	2
Duration of Present Depressive Episode (Weeks Since Onset)			
Mean	24.5	31.0	27.6
Median	16	20	16
Range	2-160	3 - 208	2 - 208
S.E.	4.5	7.0	4.1
Not Recorded	0	3	3
Previous Antidepressant Use N, (%)			
Yes	10 (27)	10 (27)	20 (27)
No	27 (73)	27 (73)	54 (73)

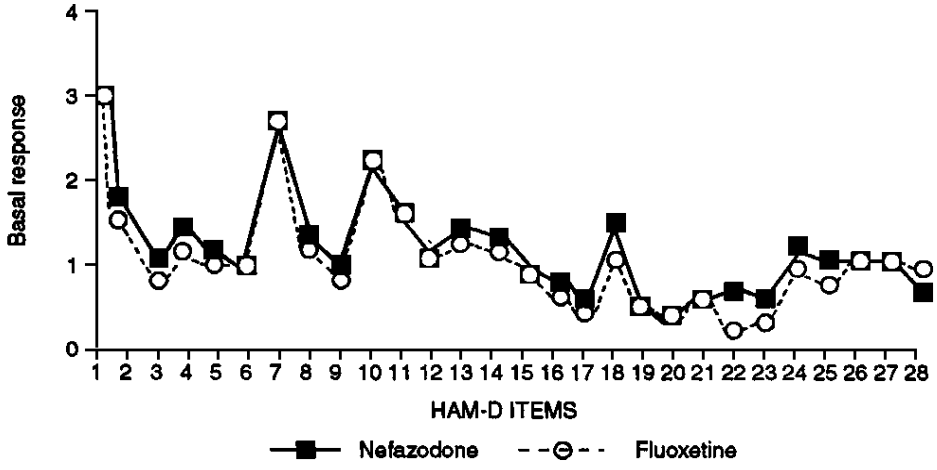

Figure 1. Individual HAM-D 28 items: Profile at baseline.

cholic type. Less than half (43%) had experienced a previous episode, and 27 % had received antidepressant drug treatment in the past. The mean age of onset of the present episode for both groups was 35.3 years and mean duration of the present episode was 27.6 weeks. None of the treatment groups differed at baseline in the overal severity of depressive symptoms. Forty-nine (66 %) of the 74 patients received concomitant medication: 26 (70%) of the fluoxetine treated patients and 23 (62%) of the nefazodone-treated patients. Twenty-five (68%) patients in the fluoxetine treatment group and 20 (54%) patients in the nefazodone treatment group received a concomitant CNS medication. The most frequently used concomitant CNS medication was a benzodiazepine. No patients received psychotropic medications that were prohibited by the protocol.

The symptom profile at baseline obtained from the individual items of the 28-items HAM-D showed that the symptom profiles of patients in the two treatment groups were similar before treatment (figure 1). The results from the 17-items HAM-D total score (LOCF data set) are presented in table 2. At endpoint, the mean change was –12.4 for the fluoxetine group and –12.3 for the nefazodone group and there was not a significant treatment by center interaction. No statistically significant-differences were observed between the nefazodone an fluoxetine treatment groups. The 95% confidence interval of –4.2 to 4.1 is fairly symmetrical around zero, showing a comparability in the change in HAM-D scores for the two treatments. Clinical significant improvement was evident by week 2 both for the nefazodone and the fluoxetine patients (figure 2) and at endpoint the two treatments produced a statistically significant change from baseline ($p < 0.1$). The analysis of the visitwise data is presented in table 3. The visitwise results show no significant differences in the HAM-D total score between groups of treatment. Like the LOCF analyses, the visitwise analyses demonstrated significant improvement by week 2 of treatment.

A summary of the efficacy results at endpoint (LOCF) is shown in table 4. Both treatment groups exhibited similar and significant improvement in the LOCF analysis. In the retardation factor there was improvement for both treatment groups but no significant differences between them. The anxiety, sleep disturbance and depressed mood factors also did not show any significant differences in the two groups. This proves a similar efficacy of the drugs in the different parameters of depressive symptomatology. The results of the analyses of the patient-rated PGA improvement scale paralleled those of the physician-rated CGI improvement scale. In the CGI severity scale a significant difference was observed at baseline: 4.5 in

TABLE 2
HAM-D17 Total Scop.E: Mean Baseline and Weekly Change and 95% Confidence Intervals on Treatment Diference. Analysis of LOCF Data Set

Variable	*Week*	*Fluoxetine (N=37)*	*Nefazodone (N=36)*	*95% Confidence Intervals**
Baseline		23.7	25.1	
Change From Baseline	1	–4.6	–5.5	(-1.2, 2.9)
	2	–8.0	–8.2	(–2.9, 3.4)
	3	–10.8	–8.8	(–5.2, 1.1)
	4	–11.8	–10.6	(–4.7, 2.4)
	6	–12.8	–12.0	(–4.4, 3.0)
	8	–12.4	–12.3	(–4.2, 4.1)

* The confidence interval is centered around the treatment difference, which is defined as, the change score for fluoxetine minus the change score for nefazodone.

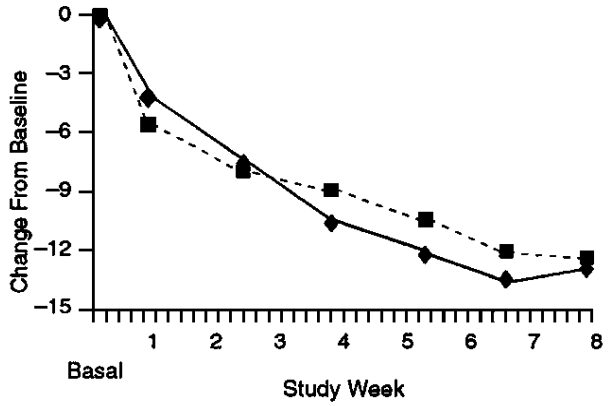

Figure 2. HAM-17 total score: Mean change from baseline last observation carried forward data set

the fluoxetine group and 4.9 in the nefazodone group ($p \leq .01$); however the results of an ANCOVA performed to account for this difference were consistent with the results of the ANOVA, finding that after adjusting for baseline severity, the mean change at week 8 was –2.0 for the fluoxetine group and –1.8 for the nefazodone group. In the analysis of the vistwise data set of this severity scale, nefazodone patients showed statistically greater improvement than fluoxetine patients at week 6 ($\bar{X} = -2.6$ vs $\bar{X} = -1.8$; $p < 0.5$). Finally, the results of the HAM-A total score showed that there was improvement in both groups but there were no significant differences between them.

Three (8%) of the nefazodone patients and 1 (3%) of the fluoxetine patients discontinued from the study because of an adverse event. Reasons for discontinuation from treatment are summarized in table 5. Twenty-nine of the 37 (78%) fluoxetine patients and 26 of the 37 (70%) nefazodone patients reported an

TABLE 3
HAM-D17 Total score: mean baseline and weekly change and 95% confidence intervals on treatmcnt difference. Analysis of visitwise data set

		Fluoxetine		*Nefazodone*		*95% Confidence*
Variable	*Week*	*N*	*Mean*	*N*	*Mean*	*Intervals**
Baseline		37	23.7	36	25.1	
Change From Baseline	1	37	–4.6	32	–5.9	(–0.8, 3.5)
	2	35	–8.0	33	–8.4	(–3.0, 3.9)
	3	31	–11.6	30	–9.1	(–5.9, 1.0)
	4	34	–12.2	33	–10.7	(–5.3, 2.2)
	6	32	–13.1	25	–14.9	(–2.3, 5.9)
	8	35	–12.6	29	–13.6	(–3.5, 5.5)

* The Confidence Interval is Centered Around the Treatment Diference, which is defined as the Change Score por Fluoxetine Minus the Change Score for Nefazodone.

TABLE 4
Summary of efficacy results at endpoint (LOCF)
Number (%) of patients

Variable	*Fluoxetine (N = 37)*	*Nefazodone (N = 36)*
HAM-D 17 Items		
Baseline Total (Mean)	23.7	25.1
Change From Baseline (Mean)		
Total Score	–12.6	–13.6
Retardation Factor	–4.3	–3.4
Anxiety Factor	–3.4	–3.5
Sleep Disturbance Factor	–1.9	–2.5
Depressed Mood Item 1)	–1.6	–1.3
Responders N *(%)*		
CGI Scale		
Physician's Opinion of Improvement	18 (49)	17 (47)
Physician's Opinion of Severity		
Baseline (Mean)	4.5	4.9
Change From Baseline (Mean)	–1.9	–1.9
PGA Scale		
Patien's Opinion of Improvement	20 (54)	18 (50)
HAM-A Score		
Baseline Total (Mean)	18.1	19.1
Changue from baseline (Mean)	–10.0	–10.0

TABLE 5
Primary reasons for discontinuation. Comparison of nefazodone and fluoxetine. Number (%) of patients

Reason *Total Sample*	*Fluoxetine* *N-37*	*Nefazodone* *N-37*	*Total* *N-74*
Completed Study	35 (95)	29 (78)	64 (86)
Lack of Efficacy	0	2 (5)	2 (3)
Adverse Experience	1(3)	3 (8)	4 (5)
Patient Withdrew Consent	1(3)	0	1 (1)
Patient Unreliable	0	1(3)	1 (1)
Other Known Cause	0	1(3)	1 (1)
Lost to Follow-Up	0	1(3)	1 (1)
Total Discontinuations	2 (5)	8 (22)	10 (14)

adverse event during the study. The adverse events that occurred most frequently (>10%) in patients receiving nefazodone were headache, insomnia, nausea, anxiety, somnolence, constipation, emotional lability, abdominal pain and dizziness. The adverse events that occurred most frequently in patients receiving fluoxetine were headache, nausea, dizziness, anxiety, insomnia, somnolence, and abdominal pain. Adverse events reported by 10% or more of the patients in either of the treatment groups are presented in table 6. One patient treated with fluoxetine took an overdose of 25 mg. of lorazepam on study day 24. The patient's only reported symptom was somnolence, she was not hospitalizad and after recovery continued in the study. One patient treated with nefazodone was hospitalizad on study day 35 for surgical repair of a right inguinal hernia. After recovering from the procedure, the patient continued uneventfully in the study. Excluding trivial findings, there was no evidence of organ toxicity based on physical examination findings or significant abnormal laboratory values. In conclusion, safety assessments revealed no evidence that nefazodone administration resulted in any medically serious adverse events or organic toxicity.

TABLE 6
Adverse events that occurred in °10% of any treatment group by body system and primary term. Comparison of nefazodone and fluoxetine

	Number(%) of Patients	
Body System/ *Primary Term*	*Fluoxetine* *(N = 37)*	*Nefazodone* *(N = 37)*
Body as a Whole		
Headache	16 (43)	16 (43)
Abdominal Pain	5 (14)	4 (11)
Asthenia	5 (14)	2 (5)
Digestive System		
Nausea	8 (22)	9 (24)
Constipation	2 (5)	5 (14)
Nervous System		
Dizziness	4 (11)	8 (22)
Anxiety	7 (19)	7 (19)
Insomnia	13 (35)	7 (19)
Emotional Lability	0	5 (14)
Somnolence	6 (16)	5 (14)

Discussion

The efficacy of nefazodone in treating moderately to severely ill patients with major depression according to DSM-III-R criteria was similar to that of fluoxetine. The analysis showed consistent improvement in symptoms of depression over the eight weeks of therapy for both drugs, as observed by the several physician and patient-rated scales. There were no statistically significant differences between the two treatments noted at any point during the study on any of the efficacy outcome measures. Also the results of the study suggest that the time of onset for the therapeutic effect was similar for the two antidepresants finding this effect by the end of the second week of treatment. Most of the patients presented a rather moderate severity of depression, and that could be explained because the majority of the cases were of non-melancholic subtype.

As demonstrated by several previous studies (13), nefazodone has a high efficacy potential at a mean dose of 400 mg. A low drop-out rate for lack of efficacy in both treatment groups is explained by the fact that the two drugs present a similar high-efficacy potential. Since a relative small number of patients were lost throughout the study, the visitwise analyses are in accord with the LOCF analyses in that the nefazodone and the fluoxetine treatment groups show a similar overall pattern of improvement. There were no differences between the treatments with respect to the symptom profile analyzed, with the exception that fewer patients in the nefazodone group required concomitant treatment with benzodiazepines, suggesting that nefazodone may be better than fluoxetine in improving some anxiety symptomatology, although this difference did not reach statistical significance.

A total of 4 patients (5% of the total sample) discontinued from the study for an adverse event related to the treatment, which shows that both drugs were well tolerated. The side-effects most commonly reported were also very similar in the two groups, without any significant difference. This finding is in accordance with previously reported studies with respect to tolerability of the drug (14). The safety of nefazodone is also determined by the finding that there were no severe side-effects during the trial, and also there were no significant alterations in the results of the laboratory tests or EKG in any patient. Side-effects, afthough

present, did not outweight therapeutic effect at any moment, nor in any case affect patient's functioning. Safety assessments revealed no evidence that nefazodone administration resulted in any medically serious adverse events or organic toxicity. As could be anticipated, both nefazodone and fluoxetine demonstrated to have a very similar side-effects profile, with a generally good tolerance.

Conclusion

The results of the study indicate that both nefazodone and fluoxetine are effective treatments of patients with moderate to severe major depression (DSM-III-R criteria). The improvement at endpoint for the nefazodone group on all of the efficacy outcome measures was comparable to that of the fluoxetine group, with no statistically significant differences. It was also found that nefazodone may be more effective in reducing some anxiety symptoms and to have a more sedative effect than fluoxetine.

Nefazodone was found to be safe and well tolerated, without any important differences in these parameters with respect to fluoxetine. In conclusion, nefazodone showed to be an excellent new antidepressant for treating major depression in terms of efficacy, tolerance and safety. Further studies are needed to characterize the efficacy of nefazodone in other forms of depression and also to evaluate its efficacy and effect over longer periods of treatment.

Supported by Bristol-Myers Squibb Pharmaceutical Research Institute, Wallingford, CT.

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