Clinical Use of Nefazodone in Major Depression: A 6-Year Perspective

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Use of Nefazodone in Major Depression

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The efficacy of antidepressants for the treatment of major depressive disorder (MDD) is based on more than 250 randomized, double-blind, controlled, acute-phase trials. Most antidepressants are considered comparably effective, although only 50% to 60% of depressed patients respond to a single medication trial.[1] Differences among the antidepressants reside primarily in safety and tolerability issues, which may impact long-term patient compliance. Efforts to establish predictors of antidepressant response have not been entirely successful; predictors often vary in definition and do not produce consistent outcomes.[2] During treatment of depression, the presence of comorbid anxiety symptoms, duration and severity of illness, and long-term tolerability can be used to select therapy and may predict ultimate outcome.

Nefazodone has been evaluated in prospective, randomized, double-blind trials in patients with documented MDD.[4–12] In two 6-week, randomized, double-blind, placebo-controlled trials, all patients had a pretreatment 17-item Hamilton Rating Scale for Depression (HAM-D-17) score of 20 or higher, and a sizable portion of the patient sample (46%–70%) also met criteria for melancholic subtype.[5,6] Nefazodone has been compared with the tricyclic antidepressants (TCAs) imipramine and amitriptyline and with various selective serotonin reuptake inhibitors (SSRIs) in acute (6- to 10-week) placebo-controlled trials and in longer-term continuation and maintenance phase trials.[4–12] Primary outcome measures typically included mean absolute and percent changes from baseline to endpoint in HAM-D score and percent responders on the Clinical Global Impressions scale (CGI) at endpoint.[4–12] Key trials are summarized in the following sections and in Table 1.[4–12]

NEFAZODONE VERSUS PLACEBO: DOSE-RANGING TRIALS

Two dose-finding studies[5,6] conducted in depressed outpatients helped establish the optimal, effective dose of nefazodone. Both were 6-week, randomized, double-blind, placebo-controlled comparisons; in 1 trial, an imipramine treatment arm also was incorporated. All patients had a pretreatment HAM-D-17 score of 20 or higher; a sizable portion of the patient sample (46%–70%) also met criteria for melancholic subtype. In the first trial, nefazodone dose ranges were 100 mg/day to 500 mg/day (high) and 50 mg/day to 250 mg/day (low).[5] Dose ranges were intentionally overlapped. Nefazodone dose ranges were similar in the second study: 100 mg/day to 600 mg/day (high) and 50 mg/day to 300 mg/day (low).[6]

At the endpoint analysis for change in HAM-D score, patients in both trials treated with the higher dose ranges of nefazodone showed significantly greater improvement than those treated with placebo or lower doses of nefazodone (Table 1). Other evaluative criteria, such as the CGI, the Inventory for Depressive Symptomatology, and the Symptom Check List-90, were significantly improved in patients receiving higher doses of nefazodone. The mean daily dose during the last treatment week in the higher dose range nefazodone group was 392 mg[6] to 460 mg.[5] Based on these and other data from phase 2/3 clinical trials, the optimal maintenance dose of nefazodone is between 300 and 500 mg/day.[8,11,13]

In an unpublished, fixed-dose, double-blind, randomized, multicenter study in 416 outpatients, the dose-response relationship of nefazodone also was evaluated (data on file, Bristol-Myers Squibb Company, Princeton, N.J., 1997). All patients met DSM-IV criteria for single or recurring nonpsychotic MDD with or without melancholic features. At endpoint, the test for linear trend in the HAM-D-17 total score was significant ($p = .024$) among the 4 randomized treatment groups (placebo vs. nefazodone 400 mg/day, 500 mg/day, and 600 mg/day). The mean change from baseline in the HAM-D-17 total score at week 8 was –10.4 and –10.3 in the 400-mg/day and 600-mg/day nefazodone groups, respectively ($.01 < p < .05$ versus placebo). The results clearly show that there was no loss of efficacy at the 600-mg/day dose.

Pooled Analyses

A pooled analysis of placebo-controlled nefazodone trials showed that 53% of patients (104/198) receiving high-dose nefazodone (400–600 mg/day) had a 50% or greater reduction in the HAM-D-17 total score at endpoint ($p = .002$) as compared to only 37% of the placebo group (73/197) (data on file, Bristol-Myers Squibb Company, Princeton, N.J.).

Another pooled analysis of data from 781 patients from short-term, placebo-controlled trials of nefazodone in the labeled dose range (300–600 mg/day) was conducted (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Many early low-dose, placebo-controlled trials and low-dose treatment arms were therefore excluded. The mean endpoint change in HAM-D-17 total score (–11.0) from baseline (24.5) was consistently significant in all groups ($p < .001$). Analysis was also conducted in a set of patients whose current episode of depression had lasted 2 years or longer. In this group, possibly treatment resistant, nefazodone showed only a trend toward efficacy ($p = .071$). Although most protocols try to exclude treatment-resistant patients, exclusion is highly dependent on the investigator's obtaining an accurate psychiatric treatment history.

Table 1. Summary of Comparative Clinical Trials With Nefazodone and Tricyclic Antidepressants in Patients With Major Depression[a]

Reference (centers)	Dosage, mg/d [mean]	N	% Withdrawals (LOE)	HAM-D-17 Scores: Baseline	HAM-D-17 Scores: Change From Baseline	% Responders[b] CGI/HAM-D-17	Overall Efficacy
7[c] (10)	NEF 100–400 [242]	54	18	27.7	–9.2	39/NR	AMI > NEF
	AMI 50–200 [124]	49	8	28.1	–16.1†	69†/NR	
8[d] (1)	NEF 200–600 [332]	39	3	22.8	–12.1‡	67**/64*	NEF = IMI > PL
	IMI 100–300 [148]	36	3	23.6	–13.0*	63*/61*	
	PL	42	10	23.4	–9.2	36/36	
9[e]	NEF 100–600 [500[f]]	41	29	29.7	–13.5**	56**/54**	NEF > PL
	PL	40	48	29.8	–6.1	25/18	
5 (1)	NEF(lo) 50–250 [242]	44	15	25.6	–8.2	52/35	NEF(hi) = IMI > PL
	NEF(hi) 100–500 [460]	46	14	25.2	–11.0*	66**/57*	NEF(lo) = PL
	IMI 50–250 [214]	45	24	25.8	–10.8*	58*/49	
	PL	45	33	25.9	–6.8	38/31	
6 (2)	NEF(lo) 50–300 [239]	78	8	25.1	–10.1	49/NR	NEF(hi) > PL
	NEF(hi) 100–600 [392]	78	3	25.4	–12.7*	58*/NR	NEF(lo) = PL
	PL	75	5	25.0	–9.5	39/NR	
10, 11 (2)	NEF 100–600 [375]	86	5	24.4	–12.0**	65**/NR	NEF > PL
	IMI 50–300 [174]	83	11	24.3	–10.2‡	53/NR	IMI ≥ PL
	PL	91	19	23.5	–8.0	41/NR	
10[d] (1)	NEF 200–600 [419]	41	NR	24.2	–8.0	63	NEF = IMI = PL
	IMI 100–300 [176]	41	NR	23.8	–8.9	63	
	PL	36	NR	24.2	–8.6	64	
12[g] (1)	NEF 100–400 [270]	37	NR	24.6	–12.1	35/NR	NEF = IMI
	IMI 50–200 [127]	41	NR	24.5	–12.9	41/NR	

[a]Adapted with permission from Davis et al.[4] All were prospective, randomized, double-blind trials of 6- or 8-week duration in outpatients unless specified otherwise. Abbreviations and symbols: AMI = amitriptyline, CGI = Clinical Global Impressions scale, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, IMI = imipramine, LOE = lack of efficacy, NEF(hi) = nefazodone high dose, NEF(lo) = nefazodone low dose, NR = not reported, PL = placebo; > = significantly ($p \leq .05$) greater efficacy, ≥ = trend ($.05 < p < .1$) toward greater efficacy.
[b]Response: at least much improved CGI or ≥ 50% reduction in HAM-D-17 score at endpoint (last observation carried forward).
[c]Inpatients; HAM-D-17 values estimated from graph.
[d]Originally part of a 2-center study, but analyzed separately because of a statistically significant site-by-treatment interaction.
[e]Inpatients.
[f]Mean modal dose.
[g]Data from 1 of a 2-center study.
*$p \leq .05$ versus placebo.
**$p \leq .01$ versus placebo.
†$p \leq .01$ versus nefazodone.
‡$.05 < p < .1$ versus placebo.

Thirty-two percent of nefazodone-treated patients experienced remission (HAM-D total score ≤ 8) as compared to 21% of placebo-treated patients ($p = .001$). In the analyses of patients with a 50% or greater reduction in HAM-D and patients with remission by study week, statistical significance took place as early as week 3 ($p = .001$) for the HAM-D response and as early week 4 for the HAM-D score of 8 or less criterion ($p = .001$).

For the 393 nefazodone recipients who achieved a 50% or greater reduction in HAM-D score at endpoint, the endpoint mean modal dose was 441 mg/day (29% at 400 mg/day, 24% at 500 mg/day, and 26% at 600 mg/day). For the 167 nefazodone patients whose endpoint HAM-D score was 8 or less, their endpoint mean modal dose was 427 mg/day (29% at 400 mg/day, 22% at 500 mg/day, and 22% at 600 mg/day).

Depression-Related Anxiety Symptoms

Comorbid anxiety symptoms are present in at least two thirds of patients with MDD. Patients who display severe anxiety symptoms are likely to have a poorer recovery.[14] Anxiety symptoms can be induced by antidepressant agents and can lead to discontinuation of therapy.[15]

Fawcett and associates[16] evaluated the effect of nefazodone on depression-related anxiety symptoms in patients with major depression. Included in their meta-analysis were 6 double-blind, placebo-controlled studies comparing nefazodone with imipramine. Anxiety was measured using the Hamiliton Rating Scale for Anxiety (HAM-A), the HAM-D anxiety factor, and 3 HAM-D sub-items (agitation, psychic anxiety, and somatic anxiety). Nefazodone and imipramine were both significantly more effective than placebo in treating depression-related anxiety symptoms ($p < .01$). Symptom relief was faster with nefazodone, however. The most compelling support for this early relief was demonstrated by the significant difference on the HAM-D agitation item (item 9) with nefazodone as compared to imipramine and placebo as early as week 1, and continued from week 3 through the remainder of treatment. Significant improvement on all anxiety scores occurred by week 4 in patients receiving nefazodone. At endpoint, imipramine had no effect on somatic anxiety.[16]

Thus, an early onset and sustained benefit of nefazodone may increase patient compliance in those suffering from depression with or without anxiety symptoms.

USE IN SPECIAL POPULATIONS

The use of an antidepressant in special populations can present a challenge for the clinician.

Advanced Age

Physiologic changes associated with aging can confound expected responses to antidepressant therapy. Such changes include decreased hepatic and renal clearance, reduced lean body mass, and increased body fat relative to muscle mass. The adage "start low and go slow" is especially pertinent when treating depressed elderly patients.[17]

Nefazodone has been assessed in 6 geriatric-only (≥ 65 years of age) controlled trials (2 versus placebo and 4 versus an active comparator) (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Methodological problems, such as inadequate nefazodone dosing and short duration of treatment, confounded the findings of these studies. However, an examination of data from more than 500 elderly patients who entered nefazodone clinical trials supports using the same doses (400-mg/day minimum) as in younger adults (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Adverse event profiles in elderly patients were similar in type and frequency to those in younger adults.

In the elderly population, selection of an agent is based on an evaluation of patient-specific risk versus benefit. Nefazodone offers advantages in the elderly population with its unique pharmacologic profile. For example, the positive effect on sleep architecture may aid the older depressed patient who has concurrent insomnia.[18] This feature may eliminate the need for adjunct sedative-hypnotic drugs that could put the patient at risk for a fall or for cognitive impairment.[19,20] Other potential benefits for the elderly include a minimal impact on weight and sexual function.[21,22]

Gender, Ethnic Group

Information describing differences in antidepressant response based on gender or ethnic group is limited. Some initial data have been reported on differences in hepatic enzyme system, impact of patient education, cyclical hormones, and sleep architecture changes.[23–26] Review of nefazodone clinical trials to evaluate potential differences in response or dosing, or both, demonstrated no differences in these populations (data on file, Bristol-Myers Squibb Company, Princeton, N.J.).

NEFAZODONE VERSUS TCAs

Nefazodone has been compared with the TCAs imipramine and amitriptyline in several 6- to 8-week randomized, double-blind, placebo-controlled comparative trials in moderately to severely depressed outpatients (Table 1).[4,5,7,8,10–12] Overall, when the mean dose of nefazodone was 300 mg/day or higher, response rates were considered comparable to those of imipramine and superior to placebo. CGI response rates were 63% to 67% with these higher doses of nefazodone and 53% to 63% with imipramine. Changes in HAM-D scores with nefazodone (≥ 300 mg/day) or imipramine were likewise comparable and also were usually significantly greater than placebo. Response rates in patients receiving lower doses of nefazodone were lower than those with higher doses. Amitriptyline was better than nefazodone in 1 study,[7] but the mean dose of nefazodone used was only 242 mg/day.

NEFAZODONE VERSUS SSRIs

Nefazodone has been compared with the SSRIs paroxetine, sertraline, and fluoxetine in 6 short-term (6- to 8-week) double-blind trials in depressed outpatients (references 4, 21, 27, 28 and data on file, Bristol-Myers Squibb Company, Princeton, N.J.) (Table 2). Nefazodone was shown to be comparable to the SSRIs; response rates were similar, whether assessed by CGI improvement or HAM-D-17 scores. The final mean dose of nefazodone in the studies ranged from 412 mg/day to 472 mg/day. Nefazodone was well tolerated, and rates of discontinuation due to adverse events were similar in all trials.

Nefazodone Versus Paroxetine

Nefazodone was compared with paroxetine in a multicenter, 8-week trial in 206 outpatients with moderate-to-severe depression.[27] Analysis of total HAM-D and Montgomery-Asberg Depression Rating Scale (MADRS) scores (Table 2) and HAM-A scores in assessable patients showed consistent improvement but no statistical differences between the groups at any point. The proportion of CGI responders also was similar for nefazodone (58%) and paroxetine (60%). Analysis of HAM-D retardation, anxiety, and sleep disturbance factors scores revealed improvement in both treatment groups, but no significant differences. Both drugs were well tolerated; 14% of nefazodone-treated patients and 13% of paroxetine-treated patients withdrew because of adverse events.

Nefazodone Versus Sertraline

Nefazodone and sertraline were evaluated in 160 outpatients with single or recurrent nonpsychotic moderate or severe major depression.[21] The impact of these antidepressants on sexual function also was examined in this 6-week trial; findings are discussed in depth elsewhere in this supplement. The mean change in HAM-D score from baseline was not statistically different between the groups at any week (Table 2). In all, 42 nefazodone recipients (59%) and 41 sertraline recipients (57%) were considered

Table 2. Selected Short-Term (6–8 week) Prospective, Randomized, Double-Blind Clinical Trials With Nefazodone and SSRIs in Outpatients With Major Depression[a]

Reference (centers)	Dosage, mg/d [mean]	Patients Assessed (N)	% Withdrawals (LOE)	HAM-D-17 Total Score		% Responders[b]	Overall Efficacy
				Baseline	Change From Baseline	CGI/PGA	
27 (20)	NEF 200–600 [472]	100	3	24.6	–9.7	58/55	NEF = PAR
	PAR 20–40 [33]	95	1	24.8	–10.5	60/61	
21 (4)	NEF 100–600 [456]	71	0	23.3	–11.6	69/59[c]	NEF = SER
	SER 50–200 [148]	72	3	23.3	–11.6	72/57[c]	
Data on file, BMS	NEF 200–600 [426]	101	1	25.3	–10.7	58/50	NEF = SER
	SER 50–200 [115]	101	2	25.6	–11.9	65/61	
Data on file, BMS	NEF 100–600 [412]	77	2	24.0	–13.6	52/60	NEF = SER
	SER 50–200 [129]	74	0	24.1	–15.2	60/52	
28	NEF 200–600 [415]	94	NR	24.8	–13.4	71/NR	NEF = FLU
	FLU 20 [20]	93	NR	24.7	–13.1	73/NR	
Data on file, BMS	NEF 100–600 [450]	78	0	25.5	–11.5	57/43	NEF = FLU
	FLU 20–40 [35]	79	0	25.9	–12.5	64/48	

[a]Adapted with permission from Davis et al.[4] and data on file, Bristol-Myers Squibb Company, Princeton, N.J. Abbreviations and symbol: BMS = Bristol-Myers Squibb Company, CGI = Clinical Global Impressions scale, FLU = fluoxetine, HAM-D-17 = 17-item Hamilton Rating Scale for Depression, LOE = lack of efficacy, NEF = nefazodone, NR = not reported, PAR = paroxetine, PGA = Patient-Rated Global Assessment, SER = sertraline, SSRIs = selective serotonin reuptake inhibitors.
[b]CGI: at least "much improved" (last observation carried forward).
[c]≥ 50% reduction in HAM-D-17 total score at endpoint.

treatment responders (≥ 50% reduction in HAM-D-17 score). Using the CGI-Doctor's Opinion of Improvement at endpoint, 49 nefazodone recipients (69%) and 52 sertraline recipients (72%) were rated as responders. Treatment discontinuation due to adverse events occurred in 19% of nefazodone recipients and 12% of sertraline recipients.

The antidepressant response of nefazodone versus sertraline was also compared in a comparative 8-week trial in 202 patients with major depression (data on file, Bristol-Myers Squibb Company, Princeton, N.J.) (Table 2). The results showed consistent and comparable relief of major depression according to HAM-D-17 scores; only the reduction in the HAM-D retardation factor was significantly better in the sertraline recipients (–3.8% vs. –3.0% for nefazodone; $.05 < p \leq .1$). Thirteen patients who received nefazodone and 24 who received sertraline discontinued the study because of an adverse event.

Similar results were obtained in another trial comparing nefazodone and sertraline in 151 highly anxious patients with depression (data on file, Bristol-Myers Squibb Company, Princeton, N.J.) (Table 2). Both antidepressants provided consistent and comparable improvements in HAM-D-17 total scores and in anxiety factor, sleep disturbance factor, retardation factor, and depressed mood scores, and in HAM-A total scores. The drugs were equally well tolerated. Study discontinuations because of adverse events occurred in 17 nefazodone recipients and 11 sertraline recipients.

Nefazodone Versus Fluoxetine

Nefazodone was compared with fluoxetine in an 8-week trial in 188 patients, 97% of whom had major depression (DSM-III-R) and 3% of whom had bipolar disorder.[28] The treatment groups showed improvement in depressive symptomatology with no significant difference between the drugs as represented in the HAM-D-17 total score (Table 2). Mean changes in MADRS total score were similar between the groups (nefazodone, –15.7; fluoxetine, –15.6) as were response rates based on CGI improvement (nefazodone, 71%; fluoxetine, 73%). Discontinuations due to adverse events occurred in 10% of the fluoxetine group and 7% of the nefazodone group.

Also, in a 6-week, double-blind trial of 158 anxious patients with major depression, nefazodone and fluoxetine both provided similar, significant relief of depressive symptoms as measured by HAM-D-17 scores (data on file, Bristol-Myers Squibb Company, Princeton, N.J.) (Table 2). The reduction in the HAM-A psychic factor score was greater in the nefazodone group at week 1 (–2.9 vs. –2.2 with fluoxetine; $.05 < p \leq .1$) and the reduction in the somatic factor score was significantly better for nefazodone at week 2 than for fluoxetine (–4.5 vs. –3.6, respectively; $p \leq .05$). Sixteen patients experienced adverse events that led to discontinuation from the study (9 nefazodone, 7 fluoxetine).

Nefazodone Versus SSRIs for Continuation Treatment

Following an initial treatment response, the risk of a recurrent depressive event is 50% after 1 episode, 70% after 2 episodes, and 90% after 3 episodes.[1] Evidence clearly supports use of continuation-phase, full-dose antidepressant medication to prevent recurrence in patients with prior episodes.

Nefazodone has been compared with the SSRIs fluoxetine and sertraline in at least 4 double-blind, multicenter, comparative parallel continuation-phase trials (Table 3) (data on file, Bristol-Myers Squibb Company, Princeton, N.J.). In each, patients with DSM-III-R–confirmed major

Table 3. Summary of 4 Continuation Phase Trials Comparing Nefazodone With a Selective Serotonin Reuptake Inhibitor in Depressed Patients[a]

Study	Duration (wk)	N	Mean Dose[b] (mg/d)	HAM-D Score[b]	% CGI Responders[b]	Discontinued Due to AE[b] (N)
Study A	46					
Nefazodone		60	421.7	10.3	97	12
Fluoxetine		60	30.7	7.4	88	2
Study B	44					
Nefazodone		57	400	4.6	82	8
Fluoxetine		70	20	4.8	79	8
Study C	46					
Nefazodone		56	393	7.1	86	9
Sertraline		61	122	6.5	82	8
Study D	20					
Nefazodone		46	422	8.2	83	7
Sertraline		49	149	9.4	92	7

[a]Data on file, Bristol-Myers Squibb Company, Princeton, N.J. Abbreviations: AE = adverse event, CGI = Clinical Global Impressions scale, HAM-D = Hamilton Rating Scale for Depression.
[b]Values at endpoint.

depression who had responded to short-term therapy (6–8 weeks) were continued on that therapy for an additional 20 to 46 weeks. Total HAM-D scores and CGI response rates were obtained. In all trials, nefazodone demonstrated comparable response rates to the SSRI comparator (fluoxetine or sertraline) and was safe and well tolerated.

NEFAZODONE VERSUS PLACEBO IN HOSPITALIZED PATIENTS

Although depression is certainly debilitating in ambulatory patients, hospitalized patients are considered to be the most severely ill and at highest risk for suicide.[29] Nefazodone has been studied in 4 trials of hospitalized, depressed patients (reference 30 and data on file, Bristol-Myers Squibb Company, Princeton, N.J.). Two of the trials included a placebo control and 2 included an active comparator.

In 1 of the placebo-controlled trials, nefazodone was superior to placebo in 120 patients hospitalized for DSM-III–diagnosed, marked-to-severe, nonpsychotic major depression (mean baseline HAM-D score = 27, CGI severity score = 5.0).[30] Patients treated with nefazodone had a significant reduction in the HAM-D-17 total score at the end of week 1 that continued through week 6 (–12.2 nefazodone vs. 7.7 placebo; $p \leq .01$). Patients receiving nefazodone also had significantly better responses for the MADRS and in HAM-D retardation, anxiety, and sleep disturbance factors. The mean nefazodone dose was 491 mg/day at the end of week 2 and 503 mg/day at week 6. Nefazodone was well tolerated; 13% of patients receiving nefazodone discontinued therapy because of adverse events, whereas 10% of patients receiving placebo did so. Fewer nefazodone-treated patients than placebo-treated patients discontinued because of lack of efficacy. These and other data (data on file, Bristol-Myers Squibb Company, Princeton, N.J.) demonstrate the efficacy and safety of nefazodone in severely depressed inpatients.

NEFAZODONE IN SEVERE, MELANCHOLIC, AND RECURRENT DEPRESSION

Various data analyses from placebo-controlled, comparative trials show that nefazodone is effective in treating patients suffering from recurrent, severe, or melancholic depression.[31–33] This subpopulation of depressed patients presents unique treatment challenges because it often has greater functional impairment, is at greater risk of suicide, and may show a lower overall treatment response.

A meta-analysis of data from 8 phase 2/3 placebo-controlled clinical trials was done to examine the antidepressant efficacy of nefazodone in patients with moderate-to-severe MDD (DSM-III-R).[31] Patients in these trials received high-dose nefazodone (up to 600 mg/day), low-dose nefazodone (up to 300 mg/day), imipramine (dose not stated), or placebo. Using the change in HAM-D score or the CGI response (much or very much improved) as outcome measures, patients receiving high-dose nefazodone or imipramine had significantly greater improvement ($p \leq .05$) than patients receiving low-dose nefazodone or placebo. Findings were similar among patients globally rated as moderately ill or most severely ill (baseline HAM-D score ≥ 27).

A second analysis performed on this database was done to assess the effects of nefazodone in the subgroup of patients with major depression of the recurrent or melancholic subtype (DSM-III-R).[33] Patients with melancholic features receiving nefazodone up to 600 mg/day or imipramine had significantly better ($p < .05$) outcomes than those receiving placebo. Patients receiving lower doses of nefazodone (up to 300 mg/day) had significantly better outcome with respect to the HAM-D score but not the CGI response. Results were similar for patients with recurrent major depression.

NEFAZODONE IN RELAPSE PREVENTION

Strong evidence exists that nefazodone can prevent relapse in patients with prior nonpsychotic depressive episodes.[22] Patients (N = 131) who had responded to acute, single-blind, 16-week treatment with nefazodone and who were in stable remission were randomly assigned to 36-week, double-blind substitution treatment with nefazodone (N = 65) or placebo (N = 66). Kaplan-Meier estimates of relapse rates (HAM-D-17 total score ≥ 18) were significantly lower in patients who continued nefazodone treatment (1.8%) than in those who received placebo (18.3%; $p = .009$). The mean modal daily dose of nefazodone was 412 mg at the end of the study. Using a secondary criterion

for relapse, discontinuation for lack of efficacy, nefazodone was again significantly better in preventing relapse than placebo (17.3% vs. 32.8%; p = .028).

USE IN COMBINATION WITH OTHER TREATMENTS FOR DEPRESSION

Information on the use of nefazodone in combination with other antidepressants is limited. Data from the recent chronic depression study discussed elsewhere in this supplement show that a combination of nefazodone and psychotherapy is highly effective in chronically depressed patients.[34]

NEFAZODONE USE IN SWITCH PATIENTS

Assuming adequate doses have been prescribed for an appropriate length of time, occasionally, it may be necessary to change antidepressant medication because of either lack of efficacy or intolerable side effects that prevent further dose escalation. Results of a 12-week, open-label, multicenter study showed that nefazodone was effective in depressed patients who could not tolerate or who did not respond to an SSRI (fluoxetine, paroxetine, or sertraline).[35] Included in this trial were 404 depressed drug-naive patients, 627 depressed patients who had received an SSRI, and 119 who had received other antidepressant drugs. Among evaluable previous SSRI users, 33% (184/565) had discontinued the SSRI because of poor response and 42% (239/565) because of intolerance. All patients received nefazodone 200 mg/day to 600 mg/day (divided); the mean dose at the end of the study in evaluable patients was about 400 mg/day.

The CGI response rate (improved or very much improved) was 87% in drug-naive patients treated with nefazodone, 79% in SSRI-intolerant patients, and 66% in prior SSRI users considered poor responders. The CGI severity of illness scores improved significantly from baseline ($p < .0001$) in all 3 groups, and all patients experienced early and sustained relief of depression-related anxiety and insomnia. At the end of the study, 9% of SSRI poor responders discontinued nefazodone because of lack of effect and 18% because of adverse events. Among SSRI-intolerant patients, 21% discontinued nefazodone because of adverse events and 10% because of lack of efficacy. Among drug-naive patients, only 1% discontinued because of lack of effect and 12% because of adverse events.[35]

SUMMARY: EFFICACY OF NEFAZODONE

Nefazodone is a phenylpiperazine antidepressant with a multimodal mechanism of action, theorized to be an antagonist at postsynaptic 5-HT_{2A} receptors and a serotonin and norepinephrine reuptake inhibitor. Its efficacy has been demonstrated in short-term trials in outpatients and inpatients with MDD. Nefazodone is significantly more effective than placebo and as effective as imipramine and SSRIs. Nefazodone is effective in patients with severe, melancholic, and recurrent depression and is effective for continuation therapy and in relapse prevention. Nefazodone provides early and sustained relief from anxiety symptoms associated with depression. It is a valuable first-line choice for the treatment of MDD.

Efficacy of Nefazodone in Chronic Depression

Martin B. Keller, M.D.

Historically, attempts to develop an appropriate classification system for depressive disorders have been challenging.[36,37] Although creation of an ideal nosology remains elusive, significant findings generated in the past 2 decades have led to an increased understanding of depressive disorders that, in turn, has contributed to the refinement and sophistication of such classification systems.[38] An objective of the DSM-IV Mood Disorders Field Trial was to enhance the classification of depression that was based typically on cross-sectional symptomatology.[39] This was accomplished by proposing an additional dimension to define major depression based on 3 longitudinal course-based specifiers: the presence or absence of preexisting dysthymia, single versus recurrent episodes, and the degree of recovery between episodes. This course-based classification system may facilitate differential subtyping of the courses of dysthymia and major depression.

Conventionally, in empirical research, the construct of chronic major depression has been categorized on the bases of the above course-based modifiers. Chronic major depression has thus become theoretically defined as (1) a major depressive episode with a duration of 2 years or longer; (2) recurrent MDD without complete remission between episodes and persistence of at least 2 years; or (3) current MDD superimposed on an antecedent dysthymic disorder (double depression) and persistence of at least 2 years. Using this system, dysthymia, although a chronic disorder, would remain a lower grade depression compared with chronic major depression.[34,40,41]

Long-term studies have examined the course of chronic depressive disorders by using a naturalistic longitudinal approach.[42] Fairly consistently, results of these naturalistic studies show that only a very small percentage of patients receive adequate treatment and that increased levels of treatment tend to improve the course of chronic depression.[43] Methodologically, however, naturalistic designs

contain significant limitations. They do not allow for controlled manipulation of treatments, therefore, cause and effect relationships cannot be established unequivocally.[44]

The next sections review some of the systematic, groundbreaking studies that have contributed to the increased understanding of chronic major depression and the benefits of antidepressant therapy over the acute, continuation, and maintenance phases of treatment. This review leads to a discussion of a new study with nefazodone, a unique trial in kind and scope because it assesses the therapeutic benefits of nefazodone, the cognitive behavioral-analysis system of psychotherapy (CBASP), and their combination for the treatment of chronic major depression.[45,46]

RESPONSE OF CHRONIC DEPRESSIVE DISORDERS TO TREATMENT

Desipramine Study

Kocsis and colleagues[47] published the first systematic, randomized clinical trial to assess the effect of pharmacotherapy for long-term maintenance of chronic depression. A total of 129 outpatients who met DSM-III-R criteria for dysthymia (40%), double depression (50%), or chronic major depression (10%) were enrolled. Three treatment phases were established: acute, continuation, and maintenance. During acute treatment, patients received open-label desipramine for 10 weeks. Patients who responded fully or partially remained on desipramine therapy during the 16-week continuation phase. Responders were randomly assigned to continue desipramine or placebo for the maintenance phase, which lasted up to 2 years.

Of the 105 patients who completed the acute phase, 51% achieved at least partial remission (33% remitted fully, 18% remitted partially), 30% did not show a significant response, and 19% discontinued treatment. The average dose of desipramine was 227 ± 70 mg/day. Further, most of the 66 responders who entered the continuation phase showed a trend toward progressive recovery versus worsening of symptoms. In fact, nearly 33% of partial responders achieved total remission at the end of the continuation phase. Overall, these results supported the assumption that maintenance treatment with desipramine would have a greater level of efficacy in preventing recurrence and sustaining interepisode recovery as compared to placebo. The risk of relapse was almost 4 times as high for patients in the placebo group as that of patients in the desipramine group (52% vs. 15%, respectively). Researchers recognized that to advance knowledge about the long-term management of depressive disorders, this study needed to be replicated in a significantly larger sample of patients.[47]

Sertraline-Imipramine Study

A study of maintenance treatment with sertraline versus imipramine evaluated for the first time the effects of SSRI therapy in chronic major depression.[40,41,48–50] The study design consisted of a 12-week double-blind acute phase, a 12-week crossover phase, a 16-week continuation phase, an 18-month maintenance phase, a 6-month postmaintenance phase, and an 18-month naturalistic follow up after subjects left or completed the randomized clinical trial. The sample size was substantial; 635 patients with chronic major depression (DSM-III-R) were randomly assigned to acute treatment with sertraline or imipramine. Patients who responded to initial pharmacotherapy continued that treatment in the continuation phase. Nonresponders were provided with the alternate treatment in the crossover phase. Like acute-phase responders, patients who responded during the crossover phase were included in the continuation phase. Lastly, in the maintenance phase, sertraline responders were randomly assigned to sertraline or placebo. Imipramine responders, on the other hand, continued treatment with imipramine. In the postmaintenance phase, responders on imipramine and sertraline treatment at 18 months were randomly assigned to placebo or to stay on active drug.

At the end of the acute phase, 58% of patients in the sertraline group and 61% of patients in the imipramine group achieved remission or a satisfactory therapeutic response.[48] A positive correlation was seen between the duration of treatment and the percentage of patients who remitted or responded satisfactorily. The combined percentage of remitters and responders was significantly higher at week 12 (59%) relative to week 8 (44%; p = .001).[48]

NEFAZODONE CHRONIC DEPRESSION STUDY

Acknowledging procedural limitations that had hampered past investigations, Keller and colleagues[34] developed a methodologically sound research design to evaluate the efficacy of psychotherapy (CBASP, a therapy expressly intended for the treatment of chronic types of depression), pharmacotherapy, or the combination in chronic major depression. This study is a landmark investigation because of its unprecedented scope and valuable contributions to the understanding of chronic depressive disorders.

Study Design

This multicenter study included 681 patients with chronic major depression. The design consisted of a 12-week acute phase, a 12-week crossover phase, a 16-week continuation phase, and a 52-week maintenance phase. Patients were randomly assigned to acute-phase treatment with nefazodone (200 mg/day in 2 divided doses to start, titrated to 600 mg/day), CBASP, or the combination (nefazodone and CBASP). Acute-phase responders remained in the same treatment group during continuation. Acute-phase nonresponders in the nefazodone group crossed over to receive psychotherapy for an additional 12 weeks. Con-

versely, nonresponders in the psychotherapy group crossed over to receive nefazodone for an additional 12 weeks. Patients who responded to the treatment to which they were crossed over remained on that treatment during the continuation phase.

Acute Phase Response and Remission Rates

Pharmacotherapy had an important effect on response rate from baseline through week 4.[34] Improvement in depressive symptomatology, demonstrated by a reduction in HAM-D-24 total score, was significantly greater for patients in the combination treatment group and the nefazodone group relative to the psychotherapy group. There was no significant difference between the combination treatment and nefazodone-only groups. Both pharmacotherapy groups demonstrated significantly more improvement than the psychotherapy group. From weeks 4 through 12, the rate of improvement in the scores as a regression slope in the combination-treatment group separated significantly from that of the nefazodone group. The rate of response increased markedly for the combination-treatment group. In addition, there was a meaningful distinction between the rate of improvement in the psychotherapy group versus that in the nefazodone group, but no difference in their outcome response. There were no significant differences between the combined-treatment group and the psychotherapy group in the rate of improvement scores for weeks 4 through 12.[34]

Total response rates (satisfactory response and remission rates) for patients who completed the 12-week acute phase were 55% (nefazodone), 52% (CBASP), and 85% (nefazodone-CBASP) ($p \leq .001$). The latter represents the highest reported rate of response for chronic major depression. General response rates for the modified intent-to-treat sample were 48% for the monotherapy groups and 73% for the combination-therapy group. Data analysis based on type of response revealed that a significantly higher percentage of patients (42%; $p < .001$) achieved full remission in the combination-therapy group compared with the CBASP-only group (24%) and the nefazodone group (22%). Remission rates for the intent-to-treat sample were 48%, 33%, and 29%, respectively.[34]

For patients who completed the 12-week acute phase, the average nefazodone dose was 520 mg/day in the nefazodone-only group and 479 mg/day in the combination therapy group. For the intent-to-treat sample, the average dose of nefazodone was 466 mg/day and 460 mg/day, respectively. Consistent with many other clinical trials, these results suggest that an antidepressant response is attained typically at a nefazodone dose between 400 mg/day and 600 mg/day.

Effects on Sleep Measures

At baseline, 597 patients reported sleep disturbances. Concomitant medications or therapies for sleep disturbances were prohibited. Treatment effects were ascertained by changes on the HAM-D sleep factor measured at baseline and at weeks 1, 2, 3, 4, 6, 8, 10, and 12.[51] From week 2 through week 12, sleep disturbances decreased significantly among patients treated with either nefazodone or nefazodone plus CBASP compared with patients treated with CBASP alone ($p \leq .05$). "Difficulties falling asleep" were significantly reduced in 55% of patients in the nefazodone group, 65% of patients in the combination-therapy group, and 35% of patients in the CBASP group. Relief of "sleep continuity disturbances" occurred in 41% of patients receiving nefazodone, 52% of patients receiving combination therapy, and 36% receiving CBASP alone. Fifty-two percent of patients in the nefazodone group, 68% in the combination-therapy group, and 41% in the psychotherapy group reported full improvement in "early morning awakening." Similar results were obtained on the Inventory of Depressive Symptomatology-Subject Rated (IDS-SR). There were no notable differences across treatment groups for hypersomnia.[51]

The improvement in depression-related insomnia observed exclusively in the nefazodone treatment groups was relatively independent of the general response to treatment, which supports the conclusions that benefits on depression-related sleep disturbances were likely mediated by nefazodone.[51]

Effects on Anxiety

Approximately 33% of the 681 enrolled patients had a past history of anxiety disorder and almost 20% presented with a coexisting anxiety disorder. Results demonstrated a strong correlation between depression and anxiety measures on the HAM-A and the HAM-D-24 scales.[52] A significantly greater reduction of depression-related anxiety symptoms occurred at weeks 2, 3, and 4, as measured by the psychic factor score of the HAM-A, for patients in the nefazodone group and the combination therapy group in relation to patients in the CBASP group. Patients who received combination therapy had significantly greater improvement in the HAM-A psychic factor score compared with patients who received either nefazodone or psychotherapy, from week 8 through week 12.[52]

Among responders, type of treatment had a significant effect on anxiety at weeks 2, 3, and 4, as measured by HAM-A total scores. Patients on nefazodone experienced significantly greater improvement than patients on either combination therapy or psychotherapy alone. After week 4, there were no significant differences across treatment groups. Consistent with prior studies, these results indicate that nefazodone may have an early therapeutic effect on anxiety symptoms associated with MDD. In general, patients with chronic major depression demonstrated a delayed improvement in anxiety symptoms. Thus, such patients might benefit from being treated initially with nefazodone and adding CBASP as needed.[52]

Effects on Sexual Function

This was the first investigation to systematically analyze the effect of pharmacotherapy versus psychotherapy on sexual functioning of patients with chronic major depression.[53] The prevalence of sexual dysfunction at baseline among these chronically depressed patients was high, as measured by the Modified Rush Sexual Inventory. Among females, 21% reported an inability to achieve orgasm and 19% reported decreased intensity of orgasm. Among male patients, 37% reported a delay in achieving orgasm or ejaculation and 34% reported decreased intensity of orgasm.

A general improvement occurred in all treatment groups from baseline through week 12 in diverse areas of sexual functioning such as desire, frequency, and satisfaction. A lower percentage of women reported an inability to achieve orgasm (12%) and decreased intensity of orgasm at the end of acute treatment (15%) as compared to baseline. Among men, less than 27% reported decreased intensity of orgasm at week 12. There were no significant differences in the degree of improvement across treatments for male patients at week 12. Overall, a higher level of improvement was found among women who received combination therapy versus women who received either monotherapy. These results[53] support prior findings[21,54,55] that treatment of depression with nefazodone does not typically affect sexual function.

CONTINUATION PHASE RESULTS

Response and Remission Rates

Patients who responded to their acute-phase treatment remained on that same treatment during the continuation phase.[56] Overall, the level of response to treatment increased over the 16-week continuation phase. Total response rates among patients were 80% in the psychotherapy group, 82% in the nefazodone group, and 90% in the combination-therapy group. Remission rates increased across treatments to 57%, 62%, and 62%, respectively. The monotherapy patients who entered the continuation phase as remitters tended to maintain response better than the significant responders and at a rate similar to that in the combination group. Overall, 68% of CBASP remitters retained remission, as did 82% of the nefazodone group, and 72% of the combination group. Among patients who entered the continuation phase as significant responders, approximately 50% improved to achieve remission. Approximately 25% of the CBASP and nefazodone monotherapy patients remained responders and about 25% experienced symptom reemergence. In comparison, only 9% of the combination treatment patients lost response. Combination treatment with nefazodone and CBASP provided better protection against symptom reemergence in nonremitted responders compared with either monotherapy.[56]

SUMMARY: EFFECTS OF NEFAZODONE IN CHRONIC DEPRESSION

Research over the past 2 decades has provided greater insight into the clinical course, treatment, and outcome of chronic forms of depression.[57] Several important findings have emerged, including the need for a longer course of treatment to achieve remission, as well as the role of maintenance treatment in preventing recurrence.

Treatment strategies involving monotherapy pharmacotherapy have yielded similar response rates of approximately 50% as have smaller, but promising psychotherapy trials.[58] However, studies evaluating combination therapy with pharmacotherapy and psychotherapy have been limited and less conclusive.[59]

The nefazodone/CBASP study is the first adequately powered study to demonstrate a clear and significant advantage for combination therapy compared with monotherapy for the acute treatment of chronic forms of depression. In addition, treatment with nefazodone, either alone or in combination with CBASP, provided earlier improvement in depressive symptoms compared with psychotherapy alone. Nefazodone and CBASP were equally effective at week 12 and endpoint, but treatment with nefazodone provided earlier and greater improvement in depression-related sleep disturbance as well as earlier improvement in anxiety symptoms. Continuation treatment provided progressive improvement in remission rates for nonremitted responders across all treatment groups. Nefazodone was well tolerated and was not associated with sexual dysfunction or significant weight changes over 28 weeks of treatment.

Effects of Antidepressants on Sleep: Focus on Nefazodone

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Abnormal sleep is one of the principal target symptoms when treating patients with MDD. Ironically, most available antidepressants have potent and often disruptive effects on sleep.[60] In the following sections, the unique and beneficial effects of nefazodone on sleep are reviewed and compared with the sleep effects of the prototypical SSRI, fluoxetine. Effects of other antidepressants on sleep also are discussed.

SLEEP DISTURBANCES IN MDD

Sleep disturbances, long associated with clinical descriptions of MDD, are incorporated into the descriptive

Table 4. Mean (SD) Effects of Nefazodone (≤ 500 mg/d, divided) and Fluoxetine (≤ 40 mg/d) on EEG Sleep Parameters in Depressed Subjects With Insomnia[a]

	Nefazodone (N = 59)		Fluoxetine (N = 57)	
Parameter	Baseline	Endpoint[b]	Baseline	Endpoint[b]
Sleep latency (min)	20.5 (20.0)	23.8 (33.1)	30.8 (28.7)	31.4 (37.7)
% Sleep efficiency	85.6 (8.8)	88.3 (9.5)*	83.8 (8.8)	81.2 (10.4)*†
Awakenings (N)	25.2 (9.2)	21.3 (9.1)**	21.9 (7.5)	29.3 (9.4)**†
% AMT	8.9 (6.9)	6.0 (5.1)**	8.9 (5.4)	10.9 (6.6)**†
% Stage 1	11.1 (5.5)	10.4 (6.2)	12.1 (7.3)	17.5 (7.8)**†
% Stage 2	53.4 (8.0)	56.6 (8.0)**	53.5 (6.6)	52.1 (8.5)†
% Stage 3/4	7.7 (6.6)	6.1 (7.4)**	7.9 (6.5)	5.6 (6.3)**
% REM	18.8 (4.5)	20.9 (4.8)**	17.5 (4.2)	14.0 (5.4)**†
REM latency (min)	88.9 (40.4)	72.1 (28.4)**	87.0 (34.1)	153.3 (56.5)**†
Reduced REM latency[c]	14%	34%	19%	0%
Time in bed (min)	447.2 (44.5)	438.6 (49.9)	436.6 (49.1)	444.7 (47.9)
Total sleep (min)	420.6 (53.0)	412.4 (63.8)	400.3 (50.2)	404.5 (58.7)

[a]Reprinted with permission from Rush et al.[18] Abbreviations: AMT = awake and movement time, EEG = electroencephalogram, REM = rapid eye movement.
[b]Last observation carried forward.
[c]Reduced REM latency (≤ 60 minutes).
*p ≤ .05 versus baseline.
**p ≤ .01 versus baseline.
†p ≤ .01 versus nefazodone change from baseline.

symptomatology and contemporary diagnostic criteria for mood disorders.[61] Approximately 90% of patients suffering from untreated MDD subjectively complain about the quality and quantity of sleep.[62] Selective rapid eye movement (REM) sleep deprivation and suppression of REM sleep by some antidepressants indicate that decreased REM sleep might have a role in effecting a positive treatment response, although REM sleep suppression alone is insufficient to explain antidepressant effects.[62] Likewise, non-REM (NREM) sleep changes do not fully explain antidepressant actions. Although many patients subjectively report improvement in sleep as they become less depressed,[63] this improvement is not consistently corroborated by electroencephalogram (EEG) studies.

ANTIDEPRESSANT EFFECTS ON SLEEP

Antidepressant medications differ in their effects on depression-related sleep disturbances.[64] Like TCAs and monoamine oxidase inhibitors, nonsedating antidepressants such as SSRIs and venlafaxine significantly disrupt sleep maintenance[64,65] and may require concomitant use of sedative-hypnotic drugs, such as benzodiazepines.[66] The SSRIs may disrupt sleep continuity (i.e., increase night awakenings and decrease actual sleep time and sleep efficiency) and suppress REM sleep. Venlafaxine has been shown to decrease sleep continuity by increasing wake time, REM latency, and stage 1 sleep time, and it decreases total REM sleep time in normal volunteers[67] and in depressed inpatients.[65] Mirtazapine, in contrast, may improve sleep parameters (i.e., decrease sleep latency and increase total sleep time and sleep efficiency) without altering REM sleep architecture in depressed patients with poor quality sleep.[68]

Nefazodone Versus Fluoxetine

The objective and subjective effects of nefazodone on major sleep parameters in normal subjects and in depressed patients with depression-related insomnia are described below.

Objective measurements. In small, open-label trials, nefazodone did not suppress REM sleep or increase REM latency in either nondepressed subjects or in depressed patients.[69–71] In 3 identical, multicenter, randomized, double-blind, 8-week trials, nefazodone (N = 64, ≤ 500 mg/day) was compared with fluoxetine (N = 61, ≤ 40 mg/day) in patients with nonpsychotic MDD and insomnia.[18,19,72] Sleep continuity parameters, such as sleep efficiency (calculated from total sleep time and time in bed), number of awakenings, and awake and movement time (AMT), as well as sleep stages, were measured.

At the study endpoint, nefazodone-treated patients had significantly increased sleep efficiency, fewer nighttime awakenings, and decreased percentage of AMT as compared to baseline (Table 4).[18] Fluoxetine-treated patients had the opposite findings. Changes between the groups were statistically different (p ≤ .01). Other significant between-group findings included differences in percentage of AMT at weeks 2, 4, and 8, number of awakenings, and sleep efficiency at weeks 4 and 8. At endpoint, nefazodone-treated patients had decreased percentage of stage 1 sleep, increased percentage of REM sleep (p ≤ .01), and reduced REM latency time (p ≤ .01) as compared to baseline. Fluoxetine-treated patients showed increased percentage of stage 1 sleep, decreased percentage of REM sleep, and increased REM latency time (each p ≤ .01). Patients in both groups had decreased percentage of stage 3/4 sleep (Table 4).

Data also were analyzed for treatment responders (endpoint HAM-D-17 score < 10).[18] Nefazodone responders had fewer nighttime awakenings, lower percentage of AMT, and less percentage of stage 1 sleep, percentage of REM sleep, and REM latency time (p ≤ .01) as compared to fluoxetine responders. Differences in sleep efficiency were not statistically significant; however, there was a trend for this parameter to increase in nefazodone responders and to decrease in fluoxetine responders.

Subjective measurements. Psychometric rating instruments used to measure subjective changes in sleep in patients taking nefazodone have included various versions of the HAM-D[73,74] and the 28-item Inventory for Depressive Symptomatology Clinician-Rated (IDS-C) and Self-Rated (IDS-SR).[75,76] The HAM-D contains 3 items pertaining to sleep that are collectively referred to as the HAM-D sleep disturbance factor. The IDS-C and IDS-SR both assess

sleep-onset difficulties, middle and late awakenings, and hypersomnia; these items are collectively referred to as the total sleep factor.

In the 3 double-blind studies described above, nefazodone produced significantly greater improvement than fluoxetine on all 3 rating scale sleep factors from baseline to endpoint.[18] The IDS-SR ratings in nefazodone-treated patients showed significant improvement over fluoxetine within the first 2 weeks of the study. Similar improvements in clinician-rated scales (IDS-C and HAM-D) occurred in patients taking nefazodone at week 2. Findings were similar in the responder subgroup; for the HAM-D and IDS-C sleep factors, nefazodone-treated patients had significant improvement over fluoxetine-treated patients at weeks 2, 4, and 8 ($p \leq .01$) and on the IDS-SR sleep factor at weeks 4 and 8 ($p \leq .02$).

As described above, nefazodone has been shown to have beneficial effects on sleep in chronically depressed patients.[34,51] Thus, nefazodone may be superior to psychotherapy in treating depressive insomnia, which raises the question of whether antidepressants that worsen EEG sleep continuity, such as the SSRIs or venlafaxine, would perform as poorly as did psychotherapy. Additional studies may answer this question.

Nefazodone Versus Paroxetine

Sharpley and colleagues[77] compared the effects of paroxetine (30 mg/day) and nefazodone (400 mg/day) on sleep in a 16-day, placebo-controlled trial in 37 volunteers. Nefazodone did not affect REM sleep and had few effects on sleep continuity. In contrast, paroxetine-treated subjects showed reduced REM sleep, increased REM latency, increased numbers of nighttime awakenings, and reduced actual sleep time and sleep efficiency. Although the study was conducted in healthy volunteers, these findings support those from trials in depressed patients that show nefazodone to have little effect on REM sleep and sleep continuity factors[71,72,78]; paroxetine appears similar to fluoxetine in this regard.

USE OF CONCOMITANT MEDICATIONS FOR DEPRESSION-RELATED SLEEP DISTURBANCES

The absence of a need to add sedative-hypnotics to nefazodone therapy to alleviate depression-related insomnia symptoms may result in significant cost savings. Lian and colleagues[3] retrospectively studied a random sample of California Medicaid prescription claims to find patients with at least 1 claim for an antidepressant during a 5-month period in 1995. The analysis focused on patients receiving concomitant anxiolytics, sedative-hypnotics, or other antidepressants during a 30-day window after the primary antidepressant was ordered. A total of 1365 patients were identified (N = 119 nefazodone, N = 418 fluoxetine, N = 352 sertraline, N = 208 paroxetine, and N = 268 venlafaxine). Fewer nefazodone-treated patients (6.7%) than paroxetine-treated patients (14.9%) received a sedative-hypnotic prescription in this study. These findings were congruent with those from a 52-week Texas Medicaid study.[66]

SUMMARY: EFFECTS OF NEFAZODONE ON DEPRESSION-RELATED SLEEP DISTURBANCES

Abnormal sleep is a primary symptom of MDD. Most available antidepressants decrease REM sleep, increase REM latency, increase stage 1 sleep (too much of which results in waking up feeling tired the next day), and decrease sleep efficiency. These EEG changes are often reflected in subjective and clinical sleep ratings. Nefazodone has beneficial effects on sleep parameters, including a minimal effect on REM sleep, positive effects on NREM sleep (e.g., decreasing the amount of stage 1 sleep), and overall improvements in sleep efficiency. Additionally and currently important in light of managed-care issues, nefazodone may provide positive pharmacoeconomic benefit due to a lower incidence of use of adjunctive sedative-hypnotic use.

Overall Conclusions

In short-term clinical trials in outpatients and inpatients with MDD, nefazodone is significantly more effective than placebo and response rates are similar to those of imipramine and the SSRIs fluoxetine, paroxetine, and sertraline. Nefazodone is effective for the treatment of severe, melancholic, and recurrent depression and also for continuation therapy and in relapse prevention. It offers unique benefits including early and sustained relief from depression-related anxiety symptoms, beneficial effects on sleep parameters and sexual functioning, and a tolerability profile that supports long-term patient compliance. Nefazodone may provide positive pharmacoeconomic benefit due to a lower incidence of adjunctive sedative-hypnotic use.

Nefazodone has demonstrated a clear and significant advantage when used in combination with CBASP for acute treatment of chronic forms of major depression. Treatment with nefazodone, alone or in combination with CBASP, provided earlier improvement in depressive symptoms compared with psychotherapy alone. Nefazodone and CBASP were equally effective at week 12 and endpoint, but treatment with nefazodone provided earlier and greater improvement in depression-related sleep disturbance as well as earlier improvement in anxiety symptoms. Continuation treatment provided progressive improvement in remission rates for nonremitted responders

across all treatment groups. In patients with chronic depression, nefazodone was well tolerated and was not associated with sexual dysfunction or significant weight changes.

Drug names: amitriptyline (Elavil and others), desipramine (Norpramin and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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