Differential Effects of Nefazodone and Cognitive Behavioral Analysis System of Psychotherapy on Insomnia Associated With Chronic Forms of Major Depression

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Background: The antidepressant nefazodone and the Cognitive Behavioral Analysis System of Psychotherapy (CBASP) were recently found to have significant, additive effects in a large multicenter study of chronic forms of major depression. As nefazodone-mediated blockade of serotonin-2 receptors may directly relieve insomnia associated with depression, we examined the more specific effects of CBASP and nefazodone, singly and in combination, on sleep disturbances.

Method: A total of 597 chronically depressed outpatients (DSM-III-R criteria) with at least 1 insomnia symptom were randomly assigned to 12 weeks of treatment with nefazodone (mean final dose = 466 mg/day), CBASP (mean = 16.0 sessions), or the combination (mean dose = 460 mg/day plus a mean of 16.2 CBASP sessions). Continuous and categorical insomnia outcomes, derived from standard clinician- and self-rated assessments, were compared.

Results: Patients receiving nefazodone (either alone or in combination with CBASP) obtained significantly more rapid and greater ultimate improvement in insomnia ratings when compared with those treated with CBASP alone. This difference was maximal by the fourth week of therapy and sustained thereafter. Combined treatment did not result in markedly better insomnia scores than treatment with nefazodone alone on most measures, although patients receiving both CBASP and nefazodone were significantly more likely ($p < .001$) to achieve ≥ 50% decrease in insomnia severity.

Conclusion: Despite comparable antidepressant efficacy, monotherapy with nefazodone or CBASP resulted in markedly different effects on the magnitude and temporal course of insomnia symptoms associated with chronic forms of major depression. Patients receiving the combination of psychotherapy and pharmacotherapy benefited from both the larger and more rapid improvements in insomnia associated with nefazodone therapy and the later-emerging effects of CBASP on the overall depressive syndrome.

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Sleep disturbances are the most prevalent of the neurovegetative symptoms of depression.[1,2] Although most classification systems include both hypersomnia and insomnia as diagnostic criteria, the latter is much more common (i.e., 70% vs. 20% incidence), particularly after young adulthood.[2,3] Depressive insomnia may be viewed as a sign of dysregulation of circadian rhythms,[4] and perturbations of serotonergic, noradrenergic, cholinergic, and peptidergic neural systems have been implicated as potential causal factors.[5,6] Importantly, sleep continuity disturbances and early morning awakening are associated with increased global severity and a greater likelihood of suicidal ideation.[1,2] Moreover, sleep deprivation resulting from insomnia may worsen the daytime neurocognitive function of depressed people and exacerbate other health problems

(i.e., arthritis, diabetes, hypertension, and obesity).[1,2,5] Persistent insomnia despite treatment often reflects an incomplete remission and may herald an impending relapse.[7] Recognition and treatment of sleep disturbance are thus important aspects of the management of depression.

Antidepressant medications differ substantially in their effects on sleep. Most antidepressants suppress rapid eye movement (REM) sleep and result in improved subjective sleep quality.[8–11] However, bupropion, nefazodone, and trazodone do not suppress REM sleep and may actually increase some REM parameters.[9–13] Antidepressants that block postsynaptic serotonin-2 (5-HT_2) receptors (e.g., amitriptyline, trazodone, nefazodone, mirtazapine) and/or have pronounced antihistaminic effects (e.g., mirtazapine, amitriptyline, doxepin, trimipramine) are the most likely to improve polysomnographic measures of sleep continuity disturbances.[8,9,11,12] By contrast, the monoamine oxidase inhibitors, selective serotonin reuptake inhibitors (SSRIs), and several of the tricyclic antidepressants (TCAs) increase nocturnal awakenings among a significant minority of depressed patients.[8–12]

Among the newer antidepressants, nefazodone has a highly favorable effect on subjective and polysomnographic measures of insomnia.[12,14–16] For example, a related series of randomized double-blind studies found that nefazodone was associated with statistically and clinically significant effects on clinical and polysomnographic measures of insomnia when compared with fluoxetine.[14–16] However, the 2 drugs had comparable overall antidepressant effects, producing similar improvements on total depressive symptom scores and response rates.

Depressed patients successfully treated with psychotherapy also report subjective improvements in sleep quality.[17–19] Thase et al.[17] reported that about one half of the patients manifesting multiple polysomnographic abnormalities at baseline experienced a normalization of sleep profiles following treatment with cognitive-behavioral therapy. The effects of cognitive or interpersonal therapies on polysomnographic measures are typically much less pronounced than those observed in studies of pharmacotherapy,[17–19] however, and there have been few direct comparisons of the impact of psychotherapy and antidepressant medication on depressive insomnia.

In the current study, a large group of chronically depressed outpatients were randomly assigned to 12 weeks of treatment with nefazodone, a form of cognitive-behavioral therapy (Cognitive Behavioral Analysis System of Psychotherapy, or CBASP),[20] or the combination of the two. As reported elsewhere,[21] both of the groups receiving nefazodone improved more rapidly than the CBASP-alone group, although the CBASP-alone group "caught up" with the nefazodone-alone group by the sixth week of treatment and the 2 monotherapies had similar response and remission rates after 12 weeks of treatment. The combined therapy group had significantly better categorical outcomes and lower symptoms scores than either monotherapy, particularly after the sixth week of therapy.[21] We now report the more specific effects of these 3 treatment strategies on insomnia associated with chronic forms of major depression. Our primary hypothesis was that patients treated with nefazodone would experience more rapid and greater overall relief of insomnia symptoms than patients treated with CBASP. We did not predict that there would be a large, additive effect for CBASP and nefazodone (as compared with nefazodone alone) on insomnia.

METHOD

Patients

The methods employed in this 12-center, multistage randomized clinical trial have been described in detail by Keller et al.[21] To summarize briefly, patients between the ages of 18 and 75 were eligible to participate if they met Structured Clinical Interview for DSM-IV Disorders[22]/DSM-III-R[23] criteria for a principal diagnosis of 1 of 3 subforms of chronic mood disorder: (1) a major depressive episode lasting at least 2 years, (2) a major depressive episode superimposed on preexisting dysthymia ("double depression"), or (3) a recurrent major depressive episode with incomplete interepisode recovery and a continuous illness duration of at least 2 years. Of note, about 20% of the study group met criteria for both chronic major depression and double depression. Patients had to score at least 20 on the 24-item version of the Hamilton Rating Scale for Depression (HAM-D-24).[24] Exclusion criteria included any history of psychotic, bipolar, or obsessive-compulsive disorder as well as dementia or seizure disorders. A past history of eating disorders led to exclusion unless there was remission for at least 1 year; a 6-month remission was required for past substance abuse disorders. Pregnancy and unwillingness to discontinue breastfeeding were exclusions. Patients with poorly controlled or serious medical disorders (e.g., metastatic cancer or recent myocardial infarction) also were excluded. Stability of physical health was confirmed by a comprehensive medical history, physical examination, laboratory screening battery, and (when clinically indicated) chest x-ray and electrocardiogram. Patients could not have failed past trials of the study interventions nor could they have failed adequate trials of 2 different types of antidepressants or 2 different courses of empirically supported psychotherapy within the preceding 3 years. All patients provided explicit written informed consent for research participation, and the study protocol was approved by the Human Subjects Review Board of each of the participating sites.

Treatment

A total of 681 patients were randomly assigned to 12 weeks of treatment with (1) CBASP alone (16 to 20 individual 45–60 minute sessions), (2) nefazodone alone (routinely initiated at 100 mg b.i.d., with a dose of 300 mg/day

Table 1. Selected Sociodemographic and Clinical Characteristics at Pretreatment[a]

Characteristic	Treatment: CBASP (N = 192)	Nefazodone (N = 201)	Combination (N = 204)	Statistical Test	df	p Value[b]
Female, %	64.1	63.7	70.1	$\chi^2 = 2.8$	2	.25
White, %	90.1	87.06	92.2	$\chi^2 = 2.8$	2	.24
Age (SD), y	44.0 (10.3)	42.3 (11.2)	44.5 (10.5)	F = 2.15	2,583	.12
Marital status, %				$\chi^2 = 7.3$	10	.70
Single	30.2	26.9	23.0			
Married	37.0	39.3	39.7			
Widowed	1.0	3.0	2.5			
Divorced	21.9	21.4	27.5			
Separated	4.2	4.0	4.0			
Cohabiting	5.7	5.5	3.4			
Depression diagnosis, %				$\chi^2 = 7.9$	6	.24
Chronic MDD	35.4	37.3	33.3			
Recurrent MDD with incomplete interepisode remission	24.0	19.4	24.0			
MDD + dysthymia (double depression)	24.0	20.4	17.2			
Chronic MDD + dysthymia	16.7	22.9	25.5			
Psychiatric history, y						
Dysthymia						
Age at onset	20.6 (14.8)	18.7 (12.6)	20.2 (13.8)	F = 0.67	2,255	.51
Duration of current episode	22.3 (15.4)	22.1 (15.3)	24.6 (15.7)	F = 0.46	2,261	.63
Major depression						
Age at onset	28.0 (13.2)	25.4 (12.9)	27.4 (13.1)	F = 1.96	2,579	.14
Duration of current episode	7.8 (10.2)	7.8 (9.3)	9.5 (9.5)	F = 0.26	2,583	.78
Depression severity						
HAM-D-24 total score	26.7 (4.8)	26.7 (5.0)	27.7 (5.1)	F = 2.17	2,583	.11
IDS-SR-30 total score	39.9 (8.5)	40.1 (9.1)	39.9 (8.6)	F = 0.61	2,568	.54
GAF score	53.9 (5.8)	53.8 (5.5)	53.4 (5.5)	F = 0.39	2,583	.68

[a]Values shown as mean (SD) unless noted otherwise. Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, GAF = Global Assessment of Functioning, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR-30 = 30-item Inventory of Depressive Symptoms-Self Report, MDD = major depressive disorder.
[b]p Values for continuous variables were computed with an analysis of variance model that included treatment, center, and (if significant) the treatment-by-center interaction as sources of variability. Those for categorical variables were computed using the Cochran-Mantel-Haenszel chi-square statistic stratified by site.

required after week 3, and subsequent titration permitted up to 600 mg/day in divided doses), or (3) the combination of both modalities. The mean (SD) final daily doses of nefazodone were 466 (144) mg and 460 (139) mg in the monotherapy and combination conditions, respectively. The mean final numbers of CBASP sessions were 16.0 (4.7) and 16.2 (4.8) in the monotherapy and combination conditions, respectively. Sedative-hypnotic medications were not permitted during study participation. More detailed descriptions of the treatment conditions are provided by McCullough[20] and Keller et al.[21]

Assessments

The HAM-D-24 was the primary outcome measure of the main study. This assessment was performed by an independent clinical evaluator without knowledge of treatment condition. The 30-item Inventory of Depressive Symptoms-Self Report (IDS-SR-30)[25] was used as a collateral measure. Both ratings were obtained at weeks 0, 1 through 4, 6, 8, 10, and 12. Satisfactory response was defined in the intent-to-treat (ITT) analyses as ≥ 50% reduction of HAM-D-24 score from baseline to endpoint. Remission was defined by a HAM-D-24 score ≤ 8 at the final 2 visits (completers) or endpoint (ITT).

The HAM-D-24 contains an insomnia factor consisting of 3 items, which measure early, middle, and late insomnia. Each item is scored 0, 1 (mild disturbance), or 2 (severe disturbance), yielding a maximum total insomnia score of 6. The total score is the primary dependent measure of this report. We also considered ≥ 50% reduction of the HAM-D-24 insomnia score to represent a significant improvement. We again used the IDS-SR-30 as a secondary outcome measure, reflecting the patients' perceptions of sleep disturbance. The IDS-SR-30 also has a 3-item insomnia factor, with item scores ranging from 0 to 4 (maximum total: 12).

Statistical Analysis

The sensitivity of a design intended to detect change in specific depressive symptoms is partly dependent on the prevalence of those symptoms prior to treatment. We therefore restricted analyses to patients who scored at least 1 point on the HAM-D-24 sleep items at week 0. Patients also had at least one post-randomization evaluation to be included in the ITT analyses. The demographic and clinical characteristics of the study group (N = 597) are summarized in Table 1. There were no significant differences across treatment groups on any variable.

Depression outcomes. Because only 88% of the original study group had insomnia, we first repeated the analyses performed by Keller et al.[21] to ensure that the main findings of the study were not altered. Response and remission rates for the completer and ITT samples were compared using Cochran-Mantel-Haenszel (CMH) chi-square tests (controlling for site). HAM-D-24 and IDS-SR-30 scores were compared using piecewise, mixed-effects linear random-effects model analyses. The error structure was specified as unstructured. The models included main effects for site, treatment, and time (weeks 0–4 and weeks 4–12), as well as site-by-treatment and treatment-by-time interaction effects. The former interaction effect, if significant, could jeopardize interpretation of results, whereas the latter interaction effect is the principal test of differences in the treatment groups within each of the 2 time periods.

Insomnia outcomes. The random-effects model analyses were repeated using HAM-D-24 and IDS-SR-30 total scores as dependent measures. Response group and the treatment-by-response group interaction terms were added to the model as fixed effects. These effects were included to examine if responders had outcomes different from those of nonresponders and to determine if this difference was treatment specific. Whenever main effects or interactions had significance values of $p < .10$, planned comparisons were performed. For the treatment-by-time interactions, pairwise comparisons of slopes were performed using t tests. For across-group differences at specific timepoints, simple 1-way analyses of variance (ANOVAs) were performed, followed by pairwise contrasts of means.

We used CMH chi-square tests to compare the proportions of patients who experienced significant improvement (i.e., ≥ 50% reduction) of HAM-D-24 insomnia ratings. Similarly, CMH chi-square tests were performed to compare probabilities that therapy would shift a patient's pretreatment HAM-D-24 insomnia item ratings from 2 (severe) to 0 (absent). When overall effects had a significance level of $p < .10$, pairwise comparisons were made using CMH chi-square tests.

RESULTS

Depression Outcomes

Response and remission rates among the 3 treatments are summarized in Table 2. As in the main report,[21] large and clinically meaningful differences in response and remission rates favored combined treatment over the monotherapies. Response and remission rates again did not differ significantly between the 2 monotherapies (see Table 2).

There were also large differences in symptom improvement on the HAM-D-24 and IDS-SR-30 depression scores, as reflected by significant treatment-by-time interactions (Table 3). Both groups receiving nefazodone improved significantly more rapidly during the first 4 weeks of treatment than the CBASP-alone group, whereas both groups receiving CBASP had a faster rate of symptom reduction than the nefazodone-alone group from week 5 onward. The combined treatment group thus benefited the most because of the temporally distinct and additive effects of CBASP and nefazodone, which as monotherapies yielded almost identical results at week 12 or endpoint.

Table 2. Clinical Response for Completers and Intent-to-Treat Samples[a]

Patient Sample	CBASP	Nefazodone	Combination	χ^2*
Completers				
Satisfactory response[b]	53 (81/154)	54 (83/153)	84 (138/164)	43.2
Remission[c]	24 (37/154)	22 (34/153)	42 (69/164)	43.3
Intent-to-treat				
Satisfactory response	48 (92/192)	48 (96/201)	74 (151/204)	36.5
Remission	32 (61/192)	33 (66/201)	49 (100/204)	36.5

[a]Response/remission values shown as % (N/total N). Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-D-24 = 24-item Hamilton Rating Scale for Depression.
[b]Satisfactory response included all patients with a ≥ 50% reduction in baseline HAM-D-24 total score, but whose exit HAM-D-24 total score was > 8.
[c]Remission was defined as an exit HAM-D-24 total score ≤ 8.
*All Cochran-Mantel-Haenszel chi-square (df = 2) values were $p < .001$. In all cases, CBASP = nefazodone < combination.

Insomnia Outcomes

Analyses of treatment effects on the HAM-D-24 and IDS-SR-30 insomnia scores are summarized in Table 4. On both scales, there were significant main effects for time, treatment, response group, and site. The pattern of improvement in insomnia scores during study treatment is shown in Figure 1. Simply put, patients taking nefazodone had greater relief of insomnia than those treated with CBASP alone, responders improved much more than nonresponders, and some sites had better patient outcomes than others. The interaction terms for treatment by response group and treatment by site were not significant and were removed from the statistical models for subsequent analyses.

The treatment-by-time interactions were significant through week 4 (see Table 4). Both nefazodone-treated groups had more rapid improvements of insomnia than the CBASP-alone group; the rate of early sleep improvement in the 2 groups receiving nefazodone did not differ significantly (see Table 4).

The treatment-by-time interactions did not reach statistical significance after week 4 (HAM-D-24 insomnia factor: $p = .08$; IDS-SR-30 insomnia factor: $p = .06$) (see Table 4). Pairwise comparisons of slopes revealed that the rate of improvement did not differ between the CBASP-alone and nefazodone-alone groups after the fourth week of treatment. However, the combination group had a greater rate of improvement of insomnia than the CBASP-alone group between weeks 4 and 12 (see Table 4).

The proportion of patients experiencing at least a 50% decrease in HAM-D-24 insomnia scores differed

Table 3. Results of Mixed Linear Model Random-Effect Analyses of Overall Depression Scores During Acute Phase Treatment[a]

Dependent Measure	Main Effects: Treatment F	df	p	Time F	df	p	Site F	df	p	Treatment-by-Time F	df	p	Improvement in Symptom Score (mean change): CBASP	Nefazodone	Combination
HAM-D-24 total score															
Weeks 0–4	0.53	2,583	.5903	459.93	1,594	.0001	4.88	11,1548	.0001	7.92	2,594	.0001	5.2	7.8	8.2[b]
Weeks 4–12	4.50	2,539	.0116	279.77	1,525	.0001	2.49	11,1321	.0043	13.42	2,525	.0001	6.9	4.8	9.7[c]
IDS-SR-30 total score															
Weeks 0–4	0.13	5,581	.8811	595.98	1,591	.0001	1.89	11,1546	.0367	7.26	2,591	.0008	8.7	12.2	12.5[d]
Weeks 4–12	1.99	2,1355	.1383	321.09	1,526	.0001	1.50	11,1355	.1260	18.83	2,526	.0001	8.1	5.6	13.6[e]

[a]Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-R-30 = 30-item Inventory of Depressive Symptoms-Self Report.
[b]Pairwise comparisons of slopes (HAM-D-24, weeks 0–4): CBASP < nefazodone (t = 3.18, df = 594, p = .002); CBASP < combination (t = 3.68, df = 594, p < .001); nefazodone = combination (t = 0.58, df = 594, p = .58).
[c]Pairwise comparisons of slopes (HAM-D-24, weeks 4–12): CBASP > nefazodone (t = 2.79, df = 525, p < .01); CBASP ≤ combination (t = 1.77, df = 525, p = .077); nefazodone < combination (t = 5.17, df = 525, p < .001).
[d]Pairwise comparisons of slopes (IDS-SR-30, weeks 0–4): CBASP < nefazodone (t = 2.67, df = 591, p < .01); CBASP < combination (t = 3.64, df = 591, p < .001); nefazodone = combination (t = 0.63, df = 591, p = .53).
[e]Pairwise comparisons of slopes (IDS-SR-30, weeks 4–12): CBASP ≥ nefazodone (t = 1.73, df = 526, p = .08); CBASP < combination (t = 3.82, df = 526, p < .001); nefazodone < combination (t = 5.97, df = 526, p < .001).

Table 4. Results of Mixed Linear Model Random-Effect Analyses of Insomnia Ratings During Acute Phase Treatment[a]

Insomnia Rating	Effects: Treatment F	df	p	Time F	df	p	Response F	df	p	Site F	df	p	Treatment-by-Time F	df	p	Improvement in Insomnia Score (mean change): CBASP	Nefazodone	Combination
HAM-D																		
Weeks 0–4	0.34	2,456	.7089	173.50	1,468	.0001	1.73	1,1298	.1884	4.15	11,1298	.0001	7.28	2,468	.0008	0.6	1.2	1.3[b]
Weeks 4–12	1.74	2,456	.1767	97.72	1,468	.0001	56.01	1,1274	.0001	1.24	11,1274	.2538	2.60	2,468	.08	0.7	0.8	1.1[c]
IDS-SR																		
Weeks 0–4	0.14	2,1322	.8688	223.15	1,484	.0001	2.74	1,1322	.0979	3.33	11,1322	.0002	7.79	2,1322	.0004	0.9	1.3	1.6[d]
Weeks 4–12	0.55	2,1303	.5778	169.20	1,484	.0001	38.92	1,1303	.0001	1.56	11,1303	.1033	2.87	2,1303	.06	0.9	1.0	1.3[e]

[a]Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-D = Hamilton Rating Scale for Depression, IDS-SR = Inventory of Depressive Symptoms-Self Report.
[b]Pairwise comparisons of slopes (HAM-D Insomnia score, weeks 0–4): CBASP < nefazodone (t = 2.99, df = 468, p = .003); CBASP < combination (t = 3.51, df = 468, p < .001); nefazodone = combination (t = 0.62, df = 468, p = .54).
[c]Pairwise comparisons of slopes (HAM-D Insomnia score, weeks 4–12): CBASP = nefazodone (t = 1.22, df = 468, p = .22); CBASP < combination (t = 2.28, df = 468, p = .02); nefazodone = combination (t = 1.12, df = 468, p = .26).
[d]Pairwise comparisons of slopes (IDS-SR Insomnia score, weeks 0–4): CBASP < nefazodone (t = 2.03, df = 1322, p = .04); CBASP < combination (t = 3.95, df = 1322, p = .001); nefazodone ≤ combination (t = 1.85, df = 1322, p = .06).
[e]Pairwise comparisons of slopes (IDS-SR Insomnia score, weeks 4–12): CBASP = nefazodone (t = 0.94, df = 1303, p = 0.35); CBASP < combination (t = 2.38, df = 1303, p = .02); nefazodone = combination (t = 1.40, df = 1303, p = .16).

significantly across the 3 treatment groups (CMH $\chi^2 = 32.72$, df = 2, p < .001). The combination treatment (73.5%, 150/204) was superior to nefazodone alone (59.2%, 119/201; CMH $\chi^2 = 9.05$, df = 1, p = .003), which in turn was superior to CBASP alone (45.3%, 87/192; CMH $\chi^2 = 7.87$, df = 1, p = .005).

The treatment strategies also differed with respect to the likelihood of producing complete relief of severe HAM-D-24 insomnia symptoms (Figure 2), although the effect on the sleep continuity disturbance did not reach significance. In each case, the ranking of treatments was combination > nefazodone > CBASP.

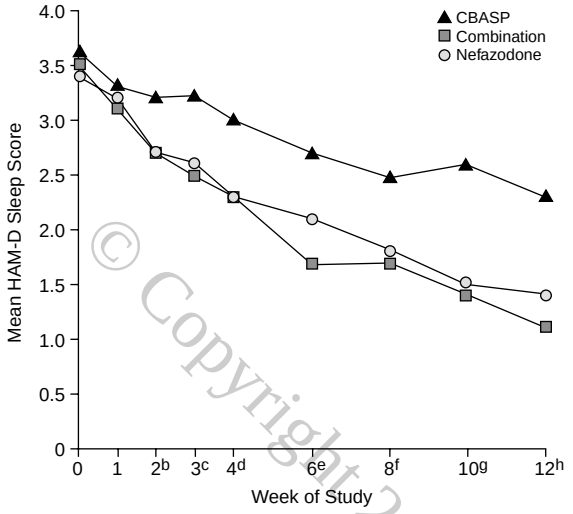
DISCUSSION

Patients receiving nefazodone therapy alone had both significantly more rapid and greater ultimate improvement of depressive insomnia than those treated with CBASP alone. Such a differential effect was observed even though the 2 monotherapies had virtually identical overall antidepressant effects by the end of acute phase therapy.

Consistent with prior studies of cognitive and interpersonal therapies,[17–19] CBASP alone had relatively modest effects on insomnia symptoms associated with depression. In fact, it took 12 weeks of psychotherapy to achieve the level of improvement in insomnia observed after only 4 weeks of nefazodone therapy.

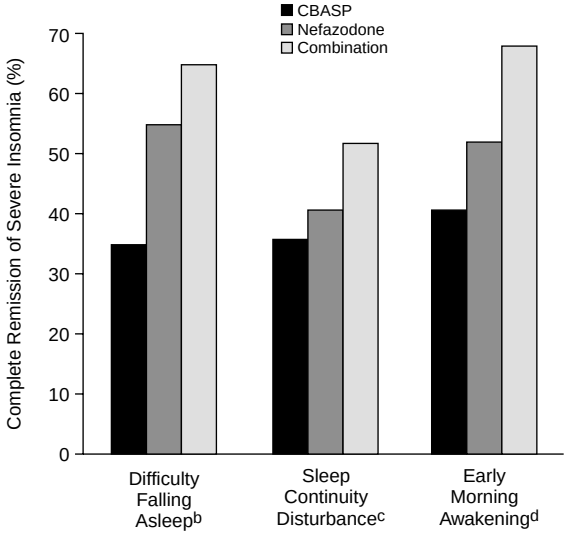
The magnitude of the effect favoring nefazodone therapy over CBASP was comparable to that which was observed in previous studies with fluoxetine.[14–16] Nefazodone-mediated relief of depressive insomnia, which is thought to result from blockade of central 5-HT_2 receptors,[12] emerged after 2 weeks of therapy, was maximal after 4 weeks, and persisted thereafter. We will examine in a future report whether or not the sleep of

Figure 1. Improvement in HAM-D Insomnia Scores During Acute Phase Treatment[a]



[a]Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-D = Hamilton Rating Scale for Depression.
[b]Overall F = 2.92, df = 2,532; p = .055; CBASP < nefazodone = combination.
[c]Overall F = 7.40, df = 2,519; p < .001; CBASP < nefazodone = combination.
[d]Overall F = 9.10, df = 2,511; p < .001; CBASP < nefazodone = combination.
[e]Overall F = 12.43, df = 2,486; p < .001; CBASP < nefazodone < combination.
[f]Overall F = 9.52, df = 2,455; p < .001; CBASP < nefazodone = combination.
[g]Overall F = 22.17, df = 2,447; p < .001; CBASP < nefazodone = combination.
[h]Overall F = 19.17, df = 2,431; p < .001; CBASP < nefazodone ≤ combination.

Figure 2. Rates of Complete Relief of Severe Insomnia Symptoms[a]



[a]Probability that someone with a pretreatment score of 2 (severe) will have a posttreatment score of 0 (absent). Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, CMH = Cochran-Mantel-Haenszel.
[b]Overall significance: CMH $\chi^2 = 16.9$, df = 2, p < .001. Pairwise comparisons: CBASP < nefazodone (CMH $\chi^2 = 7.8$, df = 1, p < .01); CBASP < combination (CMH $\chi^2 = 14.7$, df = 1, p < .001); nefazodone = combination (CMH $\chi^2 = 1.7$, df = 1, p < .28). Total Ns: CBASP, N = 81, nefazadone, N = 80; combination, N = 77.
[c]Overall significance: CMH $\chi^2 = 5.5$, df = 1, p < .06. Pairwise comparisons: CBASP = nefazodone (CMH $\chi^2 = 0.7$, df = 1, p < .39); CBASP < combination (CMH $\chi^2 = 5.7$, df = 1, p < .02); nefazodone = combination (CMH $\chi^2 = 1.5$, df = 1, p < .22). Total Ns: CBASP, N = 121; nefazadone, N = 118; combination, N = 127.
[d]Overall significance: CMH $\chi^2 = 11.6$, df = 2, p < .003. Pairwise comparisons: CBASP = nefazodone (CMH $\chi^2 = 2.1$, df = 1, p < .15); CBASP < combination (CMH $\chi^2 = 10.4$, df = 1, p < .001); nefazodone < combination (CMH $\chi^2 = 4.1$, df = 1, p = .044). Total Ns: CBASP, N = 78; nefazodone, N = 79; combination, N = 87.

CBASP-treated patients ever "catches up" throughout the continuation and maintenance phases of therapy.

The combination of nefazodone and CBASP resulted in little additive relief of insomnia symptoms when compared to treatment with nefazodone alone. A significantly greater proportion of patients in the combination group did achieve at least 50% improvement in HAM-D-24 insomnia scores, but otherwise there were few significant differences. The impact of adding CBASP to nefazodone therapy thus was primarily manifest on other aspects of the depressive syndrome unrelated to insomnia.

More than 20 years ago, DiMascio and colleagues[26] observed similar findings in a study comparing amitriptyline and interpersonal psychotherapy, singly and in combination. Although the additive effects of psychotherapy and pharmacotherapy are emphasized in traditional models of therapeutics for depressive disorders,[27] surprisingly few other studies have found large additive effects. Typically, studies of combined psychotherapy-pharmacotherapy regimens have either failed to show significant additive benefits or not examined effects on specific symptom clusters (see Rush and Thase[28] for a review). Moreover, most of these studies were not large enough to have the statistical power to detect small-to-medium additive effects.[29] With approximately 200 patients in each treatment condition, our study thus provides the strongest evidence to date that psychotherapy and pharmacotherapy can have differential, additive effects on specific aspects of the depressive syndrome.

It is not certain that these findings will generalize to other combinations of treatments or other subforms of depression. CBASP, for example, was developed primarily to address the interpersonal difficulties and problem-solving deficits that are common in chronic forms of major depression;[20] this form of psychotherapy has not been studied in more acute or episodic depressions. The bulk of the work in therapy focuses on situational analysis of the patient's goals, interpretations, and behaviors in specific interactions. Although more explicit attention to management of insomnia may be compatible with the CBASP moel,[20] we did not incorporate more specific

cognitive-behavioral strategies to deal with insomnia in this study. Techniques such as stimulus control, muscle relaxation, and sleep restriction have been shown to have symptomatic benefits comparable to those of sedative-hypnotics in short-term studies of primary insomnia.[30–33] Thus, it is possible that the effects of CBASP on insomnia symptoms could be enhanced by incorporating such focused interventions.

Most other newer antidepressants, including the SSRIs,[9,10,16] venlafaxine,[34] and bupropion,[13] do not reliably improve sleep efficiency nor increase total sleep time. These antidepressants also do not produce large or rapid improvements in depressed patients' sleep disturbances. Consequently, a different time course or pattern of additive effects might have been observed in the combined treatment group if a different antidepressant was studied.

A more theoretical issue pertains to the clinical relevance of antidepressant effects on REM sleep. On the one hand, REM sleep is thought to play an important role in the consolidation or "processing" of waking memories and affects.[35,36] From this perspective, an antidepressant that did not suppress REM sleep might actually facilitate the progress of psychotherapy. On the other hand, increased REM sleep activity has been viewed as a neurobiological correlate of the severity of the waking depressive state.[2,11] Pharmacologically mediated REM suppression thus could directly facilitate psychotherapeutic progress by dampening the intensity of dysphoric affects or intrusive cognitions. To our knowledge, there are no published studies that compare the response to psychotherapy, pharmacotherapy, and their combination in relation to effects on REM sleep. However, Thase et al.[37] did find that the combination of interpersonal psychotherapy and either imipramine or nortriptyline (i.e., potent, REM-suppressing tricyclic antidepressants) was significantly more effective than psychotherapy alone in a pooled analysis of 595 depressed outpatients. Therefore, it seems unlikely that pharmacologically mediated REM suppression could actually hinder acute phase response to psychotherapy.

The interpretation of our study is limited by several factors. First, the exclusion of many people with serious comorbidities or treatment-resistant episodes narrows generalizability. There is no reason to suspect that the relative effects of CBASP, nefazodone, and their combination would be different in an unselected population, however, and the advantage of combined treatment may have been even greater in a more complicated, harder-to-treat study group.[37]

A second limitation is that our study did not enroll patients with the "pure" dysthymia. As dysthymia is typically less symptomatically severe than major depression, there may have been a smaller additive effect for combined treatment if the full spectrum of chronic depressions was studied.

Another limitation is the reliance on relatively simple ratings of insomnia, which were extracted from depression rating scales. Polysomnography could have been used to provide a more objective appraisal of sleep disturbances, although the cost of such assessments would have been prohibitive in a study of more than 600 patients. Despite the brevity of the insomnia assessments, the validity of our findings is strengthened by the concordance of results between the self-report form of the IDS-SR-30 and the HAM-D-24 insomnia ratings, which were performed by independent, "blinded" evaluators. Nevertheless, inclusion of a more detailed clinical assessment of sleep disturbance, such as the Pittsburgh Sleep Quality Index,[38] would have strengthened the confidence in the findings.

A final shortcoming concerns our decision not to include a placebo control group. Without such a comparison group, it is not possible to state that the improvements in sleep symptoms observed in the CBASP-alone condition were greater than would be observed with the passage of time or placebo-expectancy factors. Nor is it possible to conclude that the 48% ITT response rates of the 2 monotherapies were the result of active therapeutic effects. These response rates are, however, similar to those observed in earlier, randomized trials of chronic depression,[39–45] which evaluated imipramine,[38–41,45] sertraline,[40–42] fluoxetine,[43] and desipramine.[44] Among the studies that included a control group, placebo response rates have ranged between 13%[39] and 35%.[42,43,45] Therefore, it is likely that both CBASP and nefazodone conditions would have been superior to placebo if we had included a control group. The therapeutic activity of both CBASP and nefazodone also can be inferred from the temporally distinct and additive effects observed in the combined condition.[21]

In summary, nefazodone therapy resulted in significantly more rapid and greater improvements in the insomnia symptoms of chronically depressed patients when compared with CBASP alone. These differences were apparent even though the CBASP- and nefazodone-alone groups obtained comparable improvements in overall depressive symptoms and response rates. The addition of CBASP to nefazodone pharmacotherapy did not markedly improve insomnia outcomes, although patients receiving combined treatment were more likely to achieve at least a 50% reduction of sleep disturbance than the patients treated with nefazodone alone. It will be important in future research to determine if the addition of specific sleep management strategies can further enhance outcomes of depressed patients treated with psychotherapy or, for that matter, pharmacotherapy alone.

Drug names: amitriptyline (Elavil and others), bupropion (Wellbutrin and others), desipramine (Norpramin and others), doxepin (Sinequan and others), fluoxetine (Prozac and others), mirtazapine (Remeron), nefazodone (Serzone), nortriptyline (Aventyl and others), sertraline (Zoloft), trimipramine (Surmontil), venlafaxine (Effexor).

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