Symptomatic and Syndromal Anxiety in Chronic Forms of Major Depression: Effect of Nefazodone, Cognitive Behavioral Analysis System of Psychotherapy, and Their Combination

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Background: Limited information is available on treatment response of anxiety symptoms in chronic forms of major depression. Concurrent anxiety disorders are prevalent in chronic depression, but the responsiveness of patients with such comorbidity to different treatments is largely unknown. This study investigated the comparative efficacy of nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), and their combination in improving anxiety symptoms in patients with chronic forms of major depression, including those with a concurrent anxiety disorder.

Method: 681 patients with chronic major depressive disorder (DSM-IV criteria) participated in a multicenter study of 12 weeks of acute treatment with nefazodone (N = 226), CBASP (N = 228), or the combination (N = 227). The Hamilton Rating Scale for Anxiety (HAM-A), the HAM-A psychic anxiety factor, and the anxiety/arousal subscale of the 30-item Inventory for Depressive Symptomatology-Self Report (IDS-SR-30) were used to assess anxiety symptoms.

Results: In the full sample, without controlling for change in depressive symptoms, combination therapy was superior to both monotherapies on all 3 anxiety measures both in the rate of change and at endpoint. When change in depressive symptoms was controlled for, there were no treatment differences in rate of change from baseline to week 12 on any of the 3 anxiety measures. In those patients with a concurrent anxiety disorder, however, the combination was superior to CBASP on the HAM-A and the IDS-SR-30. Nefazodone alone and combination therapy were both superior to CBASP on the HAM-A psychic anxiety factor.

Conclusion: For patients with chronic depression, combination therapy is superior to CBASP or nefazodone alone. Among patients with a concurrent anxiety disorder, nefazodone, either alone or in combination with CBASP, improves anxiety symptoms faster than CBASP alone, independent of depressive symptom reduction.

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Anxiety symptoms and disorders commonly co-occur with major depressive disorder (MDD). Among patients with a primary diagnosis of MDD, at least moderate symptoms of anxiety have been found in two thirds, and high levels of anxiety have been found in 20% to 25%.[1,2] A lifetime diagnosis of anxiety disorder has been found to occur in 58% of individuals with MDD in community-based samples[3] and a current diagnosis of anxiety disorder has been found in about half of patients seeking treatment for MDD.[2] Community surveys have found lifetime anxiety disorders to co-occur in 46% of individuals with dysthymia,[4] and surveys in psychiatric settings have found current anxiety disorder comorbidity rates of 48%[5] and lifetime rates of 71% for patients with dysthymia.[6] We have recently reported that about one third of patients with chronic forms of MDD had a lifetime diagnosis of an anxiety disorder.[7]

Comorbid anxiety has important implications for the understanding and treatment of depression. The presence of concurrent anxiety disorders is associated with an elevated risk for suicide,[8,9] poorer overall functioning,[10,11] and poorer acute[12–14] and long-term outcomes[15] in the treatment of depressive disorders.

Ideally, treatment for depressive disorders aims for remission of core depressive and associated anxiety symptoms and cognitive disturbances, as well as functional restoration. A variety of studies have documented the efficacy of antidepressant agents for the treatment of anxiety symptoms in the context of MDD and with mixed (subsyndromal) anxiety-depression states.[16–18] However, the literature on treatment response in major depression with a comorbid anxiety disorder is sparse and limited to nonchronic depression and pharmacologic management.[19–23]

Several antidepressant medications have a propensity to induce anxiety and jitteriness early in treatment.[24,25] Nefazodone, presumably because of its potent inhibition of postsynaptic serotonin-2 (5-HT_2) receptors, with moderate inhibition of both serotonin and norepinephrine reuptake, appears to positively affect both depression and anxiety.[26] Indeed, nefazodone has demonstrated greater improvement in depression-related anxiety symptoms than imipramine.[27,28]

Despite progress in understanding the treatment of anxiety within the context of acute MDD, very little is known about improvement in anxiety symptoms among patients with chronic forms of major depression. Chronic forms of major depression are associated with more psychosocial and work impairment,[29,30] increased health care utilization,[4,31] and more frequent suicide attempts and hospitalization[32] than nonchronic depression. Several recent controlled trials have documented the efficacy of acute[33–35] and maintenance medication treatments[36,37] for chronic depression. However, response rates during acute treatment have been limited (typically about 50%). More successful treatment of chronic forms of depression may require greater attention to associated symptoms, such as anxiety, that possibly contribute to the poorer overall functioning seen in this population.

As already reported,[7] combined nefazodone and psychotherapy resulted in significantly greater acute depression phase treatment response rates (73%) when compared with nefazodone alone (48%) and psychotherapy alone (48%) based on the intent-to-treat sample. These findings raise the question of whether combined treatment also influences anxiety symptoms more than do monotherapies during the course of acute treatment of chronic depression, or whether the anxiolytic effects of nefazodone alone are superior to psychotherapy treatment alone.

The current article presents a further analysis of this chronic depression data set, focusing on the comparative efficacy of nefazodone, Cognitive Behavioral Analysis System of Psychotherapy (CBASP), and combination therapy in regard to improvements in anxiety symptoms. Controlling for changes in depressive symptoms, we compared changes in anxiety symptoms among the 3 treatment conditions, especially focusing on those patients who were diagnosed as having a concurrent anxiety disorder at baseline.

METHOD

Study Design

The methods for this 12-week acute phase trial of nefazodone, CBASP, and the combination have been detailed elsewhere.[7] The following brief synopsis describes the inclusion/exclusion criteria, patient sample, treatments, and clinicians. All patients provided written informed consent prior to study participation. Patients recruited from 12 clinical sites were randomly assigned to 12 weeks of acute treatment with nefazodone, CBASP, or a combination of the two.

Patient Population

Outpatients between the ages of 18 and 75 years were included if they met DSM-IV criteria for either MDD of at least 2 years' duration, double depression (MDD superimposed on dysthymic disorder), or recurrent MDD with incomplete interepisode recovery (provided that patients were currently in a major depressive episode and the total continuous illness duration was ≥ 2 years). Diagnoses were based on the Structured Clinical Interview for DSM-IV Axis I Disorders (SCID).[38] All patients also scored at least 20 on the 24-item Hamilton Rating Scale for Depression (HAM-D-24)[39] at screening and at baseline.

Major exclusion criteria consisted of high risk for suicide; history of psychotic symptoms or schizophrenia; bipolar disorder, eating disorder within the past year, obsessive-compulsive disorder, or dementia; antisocial, schizotypal, or severe borderline personality disorder; principal diagnosis of panic, generalized anxiety, social phobia, or posttraumatic stress disorder; or any substance-related abuse or dependence disorder (except nicotine), within the past 6 months. The coadministration of any anxiolytics, sedatives, hypnotics, or any other sleep aids (pharmacologic or behavioral) during the study was prohibited.

Treatments

A manual[40] covering the review of symptoms, side effects, illnesses, and concomitant medications was used to guide psychopharmacologists in weekly clinical management visits. Each medication management visit was limited to 20 minutes, and formal psychotherapeutic interventions were prohibited. Nefazodone was initiated at

200 mg/day in 2 divided doses during the first week of treatment and titrated to 300 mg/day during week 2. After week 2, weekly incremental adjustments of 100 mg/day were made to a maximum dose of 600 mg/day to achieve maximum efficacy and tolerability.

M.D.-, Ph.D.-, and M.S.W.-level psychotherapists implemented CBASP according to a manual.[41,42] Patients attended sessions every 2 weeks during the first 4 weeks, once or twice a week during weeks 4 to 8, and weekly during the last 4 weeks of treatment for a total of 16 to 20 sessions. CBASP is a psychotherapy developed specifically for chronic forms of depression. This treatment teaches patients to examine the consequences of their behavior and to use a social problem-solving approach for resolving interpersonal conflicts. CBASP did not directly focus on methods to reduce anxiety. CBASP differs from cognitive therapy[43] by focusing primarily on interpersonal interactions (including those with therapists).

Efficacy Measures

The clinician-administered 14-item Hamilton Rating Scale for Anxiety (HAM-A)[44] was used to assess anxiety symptoms. HAM-A evaluations were performed by trained raters unaware of treatment assignment. HAM-A raters were located at separate physical locations to prevent them from seeing patients arriving at or departing from treatment sessions.

Remission status for anxiety was defined as an endpoint HAM-A total score of 8 or less. Since no uniform definition of HAM-A remission exists in the literature, a score of 8 or less was selected based on a criterion of 2 standard deviations from the mean HAM-A total score of 2.4 derived from a nonclinical sample.[45]

Because of concern that somatic symptoms predominate in the scoring of the HAM-A and might overlap highly with depressive symptoms and medication side effects, we also examined scores on the 7-item HAM-A psychic anxiety factor (mean of items 1–6, 14). In addition, the anxiety/arousal scale (items 6, 7, 15, and 23–30) of the 30-item Inventory for Depressive Symptomatology-Self Report (IDS-SR-30)[46] was employed to examine self-report of anxiety symptoms. The HAM-A was administered at baseline and weeks 1 to 4, 8, and 12. The IDS-SR-30 was administered at the same visits, plus at weeks 6 and 10.

The HAM-D-24 was used to assess depressive symptoms and to define clinical response. Antidepressant response was defined as at least a 50% decrease in HAM-D-24 total score from baseline to endpoint plus a score ≤ 15 at weeks 10 and 12 (or at endpoint for those who discontinued early).

Statistical Methods

The treatment groups were compared at baseline on continuous measures using analysis of variance and on anxiety disorder diagnoses using the Cochran-Mantel-Haenszel (CMH) test with site as the stratification variable. The relationship between HAM-A and HAM-D-24 scores at each assessment visit was examined with Pearson correlation coefficients.

For each of the 3 anxiety measures (HAM-A, HAM-A psychic anxiety factor, and IDS-SR-30 anxiety/arousal scale), the primary analysis for examining improvement over the course of the 12-week acute phase was a mixed-effects model that examined relative differences between treatments in rate of change (linear slope) from baseline to week 12, incorporating all available data. To examine treatment differences in rate of change in anxiety that were independent of previously reported[7] changes in depressive symptoms, we included HAM-D-24 total scores at each assessment visit as a time-varying covariate. The model estimated fixed effects for treatment, site, HAM-D-24 score as a time-varying covariate, and time, as well as the interaction of treatment by time. The test for differences in rates of change (controlling for HAM-D-24 score) are indicated by the treatment-by-time interaction. A random intercept and a random slope were specified. Preliminary tests for treatment-by-site interactions were not significant; therefore, these terms were excluded from the final model. The error structure was specified as unstructured in each model. The mixed-effects model was performed for the subset of patients that had a current anxiety disorder diagnosis at baseline, as well as for the full sample. Additional models were also examined in which the HAM-D-24 score was not included as a covariate.

For endpoint analyses, the patients' scores at the last visit were defined as the endpoint scores (last observation carried forward). Between-group comparisons of scores at endpoint for the HAM-A total, HAM-A psychic anxiety, and anxiety/arousal scale of the IDS-SR-30 were assessed using analysis of covariance. Endpoint scores were used as the dependent variable, while site and treatment group were included as independent variables and the relevant baseline measure was included as a covariate. Treatment-by-site interactions were again not included in the final model, since they were not significant. Pairwise comparisons of the 3 treatment groups, adjusting for baseline anxiety, were accomplished through simple contrasts. Remission rates were compared across treatment groups using a CMH test with site as the stratifying variable. Endpoint analyses of mean differences and analysis of remission rates were performed 2 ways: (1) using a formal intent-to-treat sample with baseline values carried forward for patients without a postbaseline assessment and (2) using an efficacy evaluable sample that included only those patients that had at least 1 postbaseline assessment.

Statistical tests were 2-tailed with significance declared at the .05 level.

Table 1. Test Statistics for Random Coefficient Models With and Without HAM-D-24 Score as Time-Varying Covariate: Full Sample[a]

Measure and Statistic	Treatment	Time	HAM-D-24	Time by Treatment	Site
HAM-A total score					
With HAM-D-24					
F	1.7	16.5	3939.5	0.4	9.0
df	2,665	1,665	1,2637	2,653	11,665
p	.19	< .001	< .001	.68	< .001
Without HAM-D-24					
F	3.9	782.3	NA	11.7	6.1
df	2,665	1,653	NA	2,653	11,665
p	.02	< .001	NA	< .001	< .001
HAM-A psychic anxiety					
With HAM-D-24					
F	1.9	37.2	4857.1	1.9	8.0
df	2, 665	1,655	1,2637	2,653	1,665
p	.15	< .001	< .001	.15	< .001
Without HAM-D-24					
F	4.4	951.9	NA	16.0	6.0
df	2,665	1,653	NA	2,653	11,653
p	.01	< .001	NA	< .001	< .001
IDS-SR-30 anxiety/arousal					
With HAM-D-24					
F	0.9	33.6	1400.7	2.8	1.4
df	2,663	1,651	1,3685	2,641	11,663
p	.43	< .001	< .001	.06	.15
Without HAM-D-24					
F	0.9	983.0	NA	13.1	0.6
df	2,663	1,652	NA	2,652	11,663
p	.42	< .001	NA	< .001	.83

[a]Degrees of freedom are given as numerator df, denominator df. Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR-30 = 30-item Inventory for Depressive Symptomatology-Self Report.

RESULTS

Baseline Clinical and Demographic Characteristics

Six hundred eighty-one patients with chronic forms of depression were randomly assigned to treatment with either nefazodone (N = 226), CBASP (N = 228), or a combination of the two (N = 227). Of these patients, 679 had a baseline HAM-A assessment, and 677 had a baseline IDS-SR-30 assessment. The efficacy evaluable sample (N = 657 for the HAM-A) included those randomly assigned to treatment who also had at least 1 postbaseline efficacy assessment and who attended at least 1 treatment session.

There were no significant differences between treatment groups on baseline demographic characteristics. Patients' mean ± SD age was 43 ± 10.7 years; 65% were female, 91% were white, 43% were married, and 15% were unemployed. Two hundred fifty-nine (38.0%) of 681 patients randomly assigned to treatment met DSM-IV criteria for a lifetime anxiety disorder, and 123 patients (18.1%) were diagnosed with a concurrent (during the month prior to the baseline evaluation) secondary anxiety diagnosis (primary anxiety disorder diagnoses were excluded from the study). The most common lifetime comorbid secondary anxiety diagnoses included social anxiety disorder (13.8% [94/681]) and panic disorder (8.8% [60/681]). The most prevalent current comorbid anxiety disorder diagnoses included social anxiety disorder (10.9% [74/681]), specific phobia (4.1% [28/681]), and panic disorder (2.8% [19/681]). The percentage of randomly assigned patients (N = 681) meeting diagnostic criteria for current secondary anxiety disorder was not significantly different among the treatment groups (CMH χ^2 = 5.5, df = 2, p = .06; CBASP, 14% [31/228]; nefazodone, 21% [48/226]; combination therapy, 19% [44/227]).

In addition to syndromal anxiety disorders, anxiety symptoms were also prevalent in this sample at the baseline evaluation. In the intent-to-treat sample at baseline, the mean HAM-A total score was 18.1 ± 6.1. The 3 treatment groups did not differ significantly at baseline on the HAM-A total score.

The mean HAM-D-24 total score at baseline was 26.9 ± 5.0. There were no significant differences among the treatment groups at baseline on the HAM-D-24 total score.

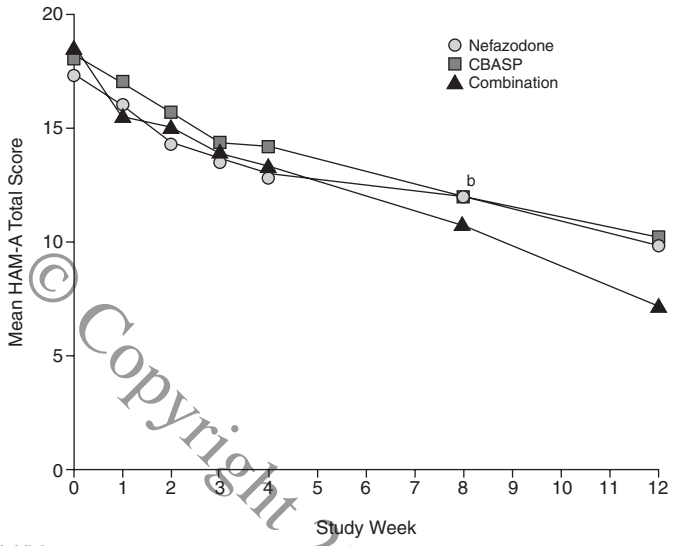
Correlations Between Anxiety and Depression Symptoms

The HAM-D-24 score was highly correlated with both the HAM-A total score (r = 0.59, p < .001) and the HAM-A psychic anxiety subscale score (r = 0.61, p < .001) at treatment baseline. Correlations were higher at the subsequent assessment visits, ranging from 0.68 to 0.82 for the HAM-D-24 total score with the HAM-A total score, and 0.73 to 0.85 for the HAM-D-24 total score with the HAM-A psychic anxiety factor, most likely because of increased variability in the measures as patients responded to treatment.

Longitudinal Analysis of Changes in Anxiety Symptoms

In the mixed-effects models conducted on the full patient sample, there were significant differences among the treatment groups in the rates of improvement in all 3 anxiety measures when HAM-D-24 score was not included in the model (Table 1). The observed means at each assessment visit for the HAM-A are presented in Figure 1 (the pattern for the other 2 measures was similar). Individual pairwise contrasts revealed that the combination was superior to both CBASP (HAM-A: F = 12.4, df = 1,653; p < .001; HAM-A psychic anxiety: F = 22.6, df = 1,653; p < .001; IDS-SR-30 anxiety/arousal: F = 15.7, df = 1,652; p < .001) and nefazodone (HAM-A: F = 21.2, df = 1,653; p < .001; HAM-A psychic anxiety: F = 24.7, df = 1,653; p < .001; IDS-SR-30 anxiety/arousal: F = 22.5, df = 1,652; p < .001). However, when the HAM-D-24 total score was included in the model as a time-varying covariate, there were no significant treatment differences (see Table 1).

Figure 1. HAM-A Total Scores: Mean Values by Treatment Group Over Time[a]



N at Each Visit:							
Nefazodone	220	202	194	193	188	157	161
CBASP	211	179	188	184	188	157	167
Combination	226	210	212	204	202	180	177

[a]Slope comparisons: combination > nefazodone, p < .001; CBASP vs. nefazodone, p = .28; combination > CBASP, p = .0005. Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-A = Hamilton Rating Scale for Anxiety.
[b]Point represents both the nefazodone and CBASP groups.

When only those patients with a secondary current anxiety disorder were examined, a different pattern of results emerged (Table 2). As with the full sample, all 3 anxiety measures showed significant treatment differences in rate of change when the HAM-D-24 score was not used as a time-varying covariate. Pairwise comparisons for this model (Table 3) revealed once again that combination therapy was superior to one or both monotherapies, with no differences between the monotherapies. In the model that included HAM-D-24 scores as a time-varying covariate (see Table 2), significant treatment differences (treatment-by-time interactions) were also evident, suggesting differential impact of the treatments on anxiety symptoms, independent of changes in depressive symptoms, for those patients with a concurrent anxiety disorder. Pairwise comparisons for the HAM-A total score and the IDS-SR-30 anxiety/arousal scale revealed combination therapy to be significantly superior to CBASP ($F = 7.5$, $df = 1,114$; $p = .007$ and $F = 8.3$, $df = 1,113$; $p = .004$, respectively) (see Table 3). For the HAM-A psychic anxiety factor, nefazodone alone was superior to CBASP ($F = 4.9$, $df = 1,114$; $p = .03$), and the combination was superior to CBASP ($F = 14.0$, $df = 1,114$; $p < .001$) (see Table 3).

Change to Endpoint

For the efficacy evaluable sample, the HAM-A total score ($F = 10.9$, $df = 2,616$, $p < .001$), HAM-A psychic anxiety factor score ($F = 17.1$, $df = 2,617$, $p < .001$), and IDS-SR-30 anxiety/arousal scale score ($F = 10.0$, $df = 2,625$; $p < .001$) all evidenced significant treatment differences on change from baseline to endpoint (Table 4). Pairwise comparisons revealed that combination therapy was significantly better than either monotherapy (all p values < .001). Similarly, comparison of the percentage of patients in each treatment group that achieved remission status on the HAM-A total score indicated a significant overall difference among the groups (CMH $\chi^2 = 15.1$, $df = 2$, $p <. 001$), with combination therapy superior to nefazodone (CMH $\chi^2 = 7.5$, $df = 1$, $p < .01$) and CBASP (CMH $\chi^2 = 13.8$, $df = 1$, $p < .001$), but no difference between the 2 monotherapies (CMH $\chi^2 = 1.0$, $df = 1$, $p = .31$). HAM-A remission rates were 60.0% (128/215) for combination therapy, 46.2% (97/210) for nefazodone, and 41.2% (87/211) for CBASP.

An identical pattern emerged in the intent-to-treat sample. The HAM-A total score ($F = 12.4$, $df = 2,664$; $p < .001$), HAM-A psychic anxiety factor score ($F = 18.2$, $df = 2,664$; $p < .001$), and IDS-SR-30 anxiety/arousal scale score ($F = 12.2$, $df = 2,662$; $p < .001$) all evidenced significant treatment differences on change from baseline to endpoint, with pairwise comparisons revealing that combination therapy was significantly better than either monotherapy (all p values < .001), but no significant differences between CBASP alone and nefazodone alone. Similarly, the intent-to-treat analysis of remission rates (carrying baseline values forward for patients without a postbaseline assessment) revealed that combination therapy was superior to nefazodone (CMH $\chi^2 = 7.8$, $df = 1$, $p < .01$) and CBASP (CMH $\chi^2 = 14.5$, $df = 1$, $p < .01$), but that there was no difference between the monotherapies (CMH $\chi^2 = 1.1$, $df = 1$, $p = .29$). Remission rates in the intent-to-treat sample were 56.4% (128/227) for combination therapy, 43.4% (98/226) for nefazodone, and 38.5% (87/226) for CBASP.

Attrition

Attrition was similar across all treatments ($\chi^2 = 1.56$, $df = 2$, $p =. 46$), with 76% of all patients completing 12 weeks (74% for nefazodone; 76% for CBASP; 79% for combination). Further information on attrition is available in an earlier report.[7]

DISCUSSION

This study underlines the importance of differentiating symptoms of anxiety in major depression from the comor-

Table 2. Test Statistics for Random Coefficient Models With and Without HAM-D-24 Score as Time-Varying Covariate: Patients With a Current Anxiety Disorder[a]

Measure and Statistic	Treatment	Time	HAM-D-24	Time by Treatment	Site
HAM-A total score					
With HAM-D-24					
F	5.32	0.001	788.3	3.77	2.35
df	2,109	1,114	1,455	2,114	10,109
p	.006	.99	< .001	.036	.02
Without HAM-D-24					
F	0.77	89.5	NA	3.80	1.24
df	2,109	1,114	NA	2,114	10,109
p	.46	< .001	NA	.03	.28
HAM-A psychic anxiety					
With HAM-D-24					
F	4.37	3.7	842.0	7.04	2.2
df	2,109	1,114	1,455	2,114	10,109
p	.015	.06	< .001	.001	.02
Without HAM-D-24					
F	0.34	117.3	NA	4.59	1.2
df	2,109	1,114	NA	2,114	10,109
p	.72	< .001	NA	.01	.33
IDS-SR-30 anxiety/arousal					
With HAM-D-24					
F	3.47	0.4	247.2	3.82	1.3
df	2,94	1,113	1,623	2,113	10,94
p	.04	.53	< .001	.03	.24
Without HAM-D-24					
F	0.20	118.3	NA	3.21	0.6
df	2,110	1,113	NA	2,113	10,110
p	.82	< .001	NA	.044	.81

[a]Degrees of freedom are given as numerator df, denominator df. Abbreviations: HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR-30 = 30-item Inventory for Depressive Symptomatology-Self Report.

bid syndromes of anxiety that may be present.[47] With the full sample of patients, our results suggested that changes in anxiety symptoms were largely confluent with changes in depressive symptoms. This agreement was evident in the longitudinal mixed models that found the same pattern of results (combined treatment superior to monotherapy) as had been found previously for changes in depressive symptoms[7] when the HAM-D-24 score was not included as a covariate. No treatment differences were found when the HAM-D-24 score was included as a covariate. Thus, for the sample as a whole, there was no evidence for any differences in the treatments in regard to anxiety symptoms that were above and beyond effects seen previously for depressive symptoms.

This similarity of findings for the HAM-A and HAM-D-24 scales is not surprising in light of the high correlations between these scales. Previous research has consistently found that HAM-A and HAM-D-24 total scores are generally highly correlated, in the range of 0.53 to 0.89.[48] Despite this redundancy, it is important to note that the advantage of combined treatment was clinically significant, as evidenced by a HAM-A remission rate that was 14 percentage points (60% vs. 46%) higher than nefazodone and 19 percentage points (60% vs. 41%) higher than CBASP. No significant difference was apparent between nefazodone alone and CBASP alone, despite the large sample size that provided good statistical power.

In contrast to the results for the full sample, when those patients with a concurrent anxiety disorder were examined, there was evidence for treatment differences that were not simply redundant with the previously reported changes in depressive symptoms. The pattern of treatment differences suggested a specific medication effect, most clearly evident on psychic anxiety. This medication effect was demonstrated by the superiority of nefazodone, and combined treatment, to CBASP alone on the HAM-A psychic anxiety factor. The evidence for a specific medication effect on the HAM-A total and the IDS-SR-30 anxiety/arousal factor was less compelling, perhaps because these scales are weighted by somatic symptoms that may be affected by medication side effects (hence, less change relative to psychic anxiety symptoms). Combined treatment, however, was consistently not different from nefazodone alone, but superior to CBASP on all 3 anxiety measures.

What might explain the overall pattern of findings? Consistent with other reports of the anxiolytic effects of nefazodone,[27,28] the finding of faster rate of change for combined treatment and nefazodone alone (for psychic anxiety) in those patients with a concurrent anxiety disorder may be a function of the specific neurochemical influences of nefazodone, such as antagonism of the 5-HT_2 receptor.[26] Relative to nefazodone, CBASP may initially increase anxiety, particularly psychic anxiety, because the treatment challenges patients' preexisting maladaptive interpersonal thoughts and behaviors. Furthermore, CBASP was developed for the treatment of chronic depression and contains no techniques directed specifically toward the treatment of anxiety. In fact, slope coefficients for CBASP were actually positive for all 3 measures, indicating relative increases in anxiety over time, once the relationship between anxiety symptoms and depressive symptoms was controlled for. In patients without a concurrent anxiety disorder, anxiety symptoms may be more closely tied to the major depressive disorder; therefore, changes in these anxiety symptoms parallel changes in depressive symptoms. Once the anxiety symptoms cross a threshold sufficient to be considered a separate syndrome, specific treatment may be required for efficacy. This would also suggest that the efficacy of CBASP may be enhanced by the addition of targeted cognitive-behavioral techniques aimed at anxiety in those with a comorbid anxiety disorder.

Given the prevalence of comorbid anxiety disorders in chronic depression, consideration of treatment options should take into account efficacy on a broad spectrum of

Table 3. Slope Estimates and Treatment Contrasts for Those Patients With a Current Anxiety Disorder[a]

Measure	CBASP Slope (SE)	Combination Therapy Slope (SE)	Nefazodone Slope (SE)	CBASP vs Combination F	df	p	CBASP vs Nefazodone F	df	p	Combination vs Nefazodone F	df	p
HAM-A total score												
With HAM-D-24	0.153 (0.088)	–0.133 (0.069)	–0.019 (0.068)	7.5	1,114	.007	2.6	1,114	.11	1.6	1,114	.21
Without HAM-D-24	–0.649 (0.147)	–0.935 (0.112)	–0.494 (0.112)	2.4	1,114	.12	0.7	1,114	.42	7.4	1,114	.008
HAM-A psychic anxiety												
With HAM-D-24	0.010 (0.008)	–0.023 (0.006)	–0.010 (0.006)	14.0	1,114	.0003	4.9	1,114	.03	2.9	1,114	.09
Without HAM-D-24	–0.061 (0.013)	–0.096 (0.010)	–0.055 (0.011)	4.7	1,114	.03	0.1	1,114	.75	8.0	1,114	.006
IDS-SR-30 anxiety/arousal												
With HAM-D-24	0.133 (0.156)	–0.326 (0.106)	0.019 (0.130)	8.3	1,113	.004	3.0	1,113	.086	1.8	1,113	.18
Without HAM-D-24	–0.652 (0.106)	–0.661 (0.079)	–0.391 (0.084)	0.0	1,113	.95	3.7	1,113	.06	5.4	1,113	.02

[a]Degrees of freedom are given as numerator df, denominator df. Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-A = Hamilton Rating Scale for Anxiety, HAM-D-24 = 24-item Hamilton Rating Scale for Depression, IDS-SR-30 = 30-item Inventory for Depressive Symptomatology-Self Report.

Table 4. HAM-A Total, HAM-A Psychic Anxiety, and IDS-SR-30 Anxiety/Arousal Mean Values for Baseline, Endpoint, and Adjusted Change[a]

Scale	Treatment Group: Nefazodone	CBASP	Combination
HAM-A total			
Baseline	17.4 ± 6.1 (220)	18.2 ± 6.1 (211)	18.7 ± 6.2 (226)
Endpoint	10.5 ± 7.1 (210)	10.9 ± 7.1 (211)	8.3 ± 6.6 (215)
Adjusted change	–7.4	–7.4	–10.0
HAM-A psychic anxiety			
Baseline	1.7 ± 0.5 (220)	1.7 ± 0.5 (211)	1.8 ± 0.5 (226)
Endpoint	1.0 ± 0.6 (210)	1.0 ± 0.7 (212)	0.7 ± 0.6 (215)
Adjusted change	–0.73	–0.70	–1.01
IDS-SR-30 anxiety/arousal			
Baseline	13.9 ± 4.8 (216)	13.5 ± 4.7 (209)	13.9 ± 4.3 (221)
Endpoint	8.1 ± 5.6 (218)	7.8 ± 5.6 (215)	6.2 ± 5.2 (222)
Adjusted change	–5.6	–5.8	–7.6

[a]All values except adjusted change expressed as mean ± SD (N). Baseline and endpoint mean values are based on observed cases at each assessment. Adjusted change scores are based on a sample that had both baseline and endpoint scores and have been adjusted for site and baseline values of the dependent variable. All within-treatment comparisons of change from baseline to endpoint were statistically significant ($p < .001$) using paired t tests. Abbreviations: CBASP = Cognitive Behavioral Analysis System of Psychotherapy, HAM-A = Hamilton Rating Scale for Anxiety, IDS-SR-30 = 30-item Inventory for Depressive Symptomatology-Self Report.

outcomes, including reduction in anxiety symptoms. Clinical decision making needs to also consider the prevention of relapses and recurrences, particularly for patients with chronic or recurrent depression. Results of the continuation and maintenance phases of this project will examine the impact of comorbid anxiety disorders on the long-term management of chronic forms of major depression for patients treated with CBASP, nefazodone, or their combination.

Limitations to the current investigation include the potential bias due to differential treatment expectancies that may occur because patients were not masked to treatment. In addition, no placebo control group was used, leaving open the question of placebo response in this population. Finally, the sample evaluated met a large number of psychiatric and medical exclusion criteria and was primarily white; therefore, results may not generalize broadly.

In summary, our findings suggest that, for those patients with a concurrent anxiety disorder, combined treatment for chronic depression yields greater improvements in anxiety symptoms than CBASP. In addition, nefazodone, either alone or in combination with CBASP, appears to produce a greater rate of change in psychic anxiety symptoms than CBASP, independent of changes in depressive symptoms.

Drug name: nefazodone (Serzone).

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