Open Trial of Nefazodone for Combat-Related Posttraumatic Stress Disorder

Michael A. Hertzberg, M.D.; Michelle E. Feldman; Jean C. Beckham, Ph.D.; Scott D. Moore, M.D., Ph.D.; and Jonathan R. T. Davidson, M.D.

Background: Because of its ability to block 5-HT_2 receptors postsynaptically and inhibit 5-HT reuptake presynaptically and/or its enhancement of sleep quality, nefazodone may be useful for symptom management in posttraumatic stress disorder (PTSD) patients.

Method: Ten patients with combat-related DSM-IV posttraumatic stress disorder (PTSD) entered an open-label 12-week trial of nefazodone with a 4-week follow-up, beginning with 100 mg/day and increasing as necessary to achieve a maximal response or until reaching a maximum dosage of 600 mg/day.

Results: Nefazodone was well tolerated, and no significant changes in sexual function were reported. Based on Clinical Global Impressions-Improvement scores, all 10 patients were rated as much improved. All PTSD symptoms (except self-reported PTSD reexperiencing symptoms), sleep, and clinician-rated depression significantly improved at week 12. At follow-up, significant changes were maintained, and self-reported PTSD reexperiencing symptoms had also significantly improved. Effect sizes for all changed symptoms were moderate to large at week 12 and at follow-up. Self-reported and clinician-rated anger significantly improved. Self-reported depression failed to improve. Improvement in social and occupational functioning was minimal.

Conclusion: These preliminary data suggest that nefazodone may be effective in reducing the 3 primary PTSD symptom clusters and may be particularly helpful in improving sleep and decreasing anger.

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Received July 9, 1997; accepted Jan. 12, 1998. *From the Department of Psychiatry, Duke University Medical Center (Drs. Hertzberg, Beckham, Moore, and Davidson), and the Durham Veterans Affairs Medical Center (Drs. Hertzberg, Beckham, and Moore, and Ms. Feldman), Durham, N.C.*

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Reprint requests to: Michael A. Hertzberg, M.D., DVAMC, 116A, 508 Fulton Street, Durham, NC 27705.

It has been estimated that 13% to 17% of Vietnam veterans suffer from current posttraumatic stress disorder (PTSD).[1,2] A recent epidemiologic study has indicated that more than one third of people with lifetime PTSD fail to recover even after many years.[3] Several biological models have been proposed as contributing significantly to PTSD, with alterations in noradrenergic and serotonergic functioning being associated most prominently with PTSD development.[4,5]

There is no definitive pharmacotherapy for PTSD, although multiple agents have been studied and have produced variably beneficial effects for PTSD symptoms and associated anxiety and depressive symptoms.[5–7] These include antidepressants (monoamine oxidase inhibitors [MAOIs], tricyclic antidepressants [TCAs], and selective serotonin reuptake inhibitors [SSRIs]), adrenergic agonists and antagonists (propranolol), antimanic or anticonvulsant drugs (carbamazepine, lithium, and valproic acid), and benzodiazepines (alprazolam). The SSRIs have recently received the most attention in the pharmacologic treatment of PTSD.[8–14] However, the SSRIs have been shown to cause sexual dysfunction, which can compromise treatment compliance.[15] Furthermore, while the antidepressant and anxiolytic effects of the SSRIs are well studied, their benefit for the treatment of insomnia is unclear.[16,17] Sleep disturbances are common in PTSD patients and often occur in association with nightmares of the traumatic event and with disturbances of rapid eye movement (REM) sleep.[18]

Nefazodone is a phenylpiperazine derivative that is structurally and pharmacologically distinct from TCAs, SSRIs, and MAOIs.[19,20] Pharmacologically, nefazodone exhibits primary serotonergic action by blocking 5-HT_2 receptors postsynaptically, but also inhibits 5-HT reuptake presynaptically. These serotonergic actions may indirectly affect other serotonin receptors, resulting in enhanced serotonergic neurotransmission. Chronic treatment with nefazodone has also been shown to down-regulate 5-HT_2 receptors. Nefazodone may therefore be effective for PTSD directly because of 5-HT_2 blockade and serotonin reuptake inhibition and/or enhancement of sleep quality.[19–22] However, there is increasing evidence for a serotonergic mechanism in PTSD. Confirmation of a serotonergic agent other than the SSRIs in the treatment of PTSD would further implicate a serotonergic mechanism in PTSD.

In a recent report, we documented that trazodone was helpful in decreasing PTSD symptoms and particularly beneficial in increasing sleep duration.[23] However, the sample size was too small to conduct statistical significance tests. Nefazodone's effect on sleep has been only minimally studied to date, but has been shown to increase sleep quality, relieve insomnia, and reduce night awakenings in depressed patients.[21,22,24] In our previous work, we found increased sleep quality and duration with trazodone treatment in PTSD patients. Trazodone and nefazodone have been compared in only 1 small-scale study, in which trazodone was found to decrease the percentage of REM sleep time, whereas nefazodone increased total REM sleep time.[21]

Nefazodone has been evaluated in several placebo- and active-controlled comparative studies that have demonstrated the antidepressant efficacy of the drug and the reduced potential for associated adverse effects. Compared with sertraline (which was associated with adverse effects on sexual function and performance in both sexes), nefazodone had no adverse effects on sexual function.[25]

The purpose of the current small-scale trial of nefazodone was to investigate possible benefits for PTSD and related symptomatology in patients with chronic combat-related PTSD. It was hypothesized that (1) the medication would be well tolerated (including no significant change in sexual functioning), (2) overall PTSD symptoms would improve, and (3) sleep would be enhanced.

METHOD

Patients were recruited from the PTSD outpatient treatment program at the Durham Veterans Affairs Medical Center in May 1996 for an open-label 12-week trial of nefazodone with a 4-week follow-up. All patients gave their consent to participate after the procedures and possible side effects were explained to them. The study was begun in May 1996 and completed in March 1997. Patients were not paid for participation. All patients met DSM-IV criteria for a current diagnosis of PTSD as determined by the Clinician Administered PTSD Scale, Diagnostic Version (CAPS-1).[26] Comorbid Axis I diagnoses were determined by the first author (M.A.H.) on the basis of a clinical interview and a record review.

Symptoms were assessed by clinician ratings and self-report scales including the Davidson Trauma Scale (DTS, a new PTSD self-report scale for which there is strong reliability and validity),[27] the Pittsburgh Sleep Quality Index (PSQI),[28] the Beck Depression Inventory (BDI),[29] the 24-item Hamilton Rating Scale for Depression (HAM-D),[30] the DSM-IV Global Assessment of Functioning Scale (GAF),[31] and the CAPS. The PSQI measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, and sleep disturbances and daytime drowsiness. The Clinician Global Impressions-Improvement[32] (CGI-I) scale primarily emphasized the patient's PTSD symptoms but also took into account overall function. The final CGI-I scores were used as the basis for distinguishing treatment responders and nonresponders. Responders were those with final CGI-I scores of either 1 or 2 (i.e., much or very much improved), whereas nonresponders were defined on the basis of having a final CGI-I score of 3, 4, 5, or 6 (i.e., minimally improved, no change, minimally worse, much worse, respectively). For descriptive purposes, all participants completed the Combat Exposure Scale[33] and the Mississippi Scale for Combat-Related PTSD (MISS).[34]

During the treatment phase for each group, treatment was begun at a dosage of 100 mg (50 mg b.i.d.) for the first week. The dosage was increased 100 mg every 2 weeks. The dosage for 1 patient was increased at a slower rate owing to minor jitteriness, which subsequently resolved. No patient failed to achieve a therapeutic dose owing to side effects. The mean therapeutic dose was 490 mg/day (range, 300–600 mg/day). So that medication compliance could be evaluated, patients completed a daily medication log. In addition, pills were counted at each visit, and compliance for each visit was calculated by dividing the number of pills taken by the number of pills prescribed. The mean medication compliance rate was 98%, with a range of 93%–100%. Somatic complaints were rated by means of a 34-item checklist rated on a 4-point Likert scale.[23] This checklist was presented to each patient at baseline and then repeated at each visit. No subject reported a substantial increase in somatic complaints, including sexual dysfunction. All 10 subjects completed baseline (week 0) and posttreatment (week 12) measures, and 9 completed follow-up (week 16) measures. All subjects continued the medication during the follow-up period. Patients were seen weekly in weeks 0–4, biweekly in weeks 4–8, at week 12, and then at week 16.

RESULTS

Description of the Sample

Nine patients were male Vietnam veterans, and 1 was a male Persian Gulf veteran. The mean Combat Exposure Scale score was 26 (moderate-heavy combat) with a range of moderate (12) to heavy (39). Forty percent were of African American descent, and the remainder were white. The mean MISS score[34] for the sample was 129. The mean age was 46 years (range, 31–51 years). All patients had a history of comorbid major depression. Of the 10 patients included in the study, 2 had no comorbid diagnoses, 2 had a past history of polysubstance abuse, 1 had major depressive disorder in remission, and 7 met criteria for a major depressive episode. At the end of the study, 3 no longer met criteria for a current major depressive episode. Seven of the patients were already service-connected (e.g., receiving monetary compensation for a disorder) for

Table 1. Means, Standard Deviations, Effect Sizes, and Analyses of Variance for Target Symptoms During Nefazodone Treatment of 10 PTSD Patients*

	Baseline (N = 10)		Week 12 (N = 10)		Baseline vs Week 12 (df = 2,18)			Week 16 (follow-up) (N = 9)		Baseline vs Week 16 (df = 2,16)		
Measure	Mean	SD	Mean	SD	Effect Size	F	p Value	Mean	SD	Effect Size	F	p Value
PTSD symptoms												
CAPS total	82.9	17.8	56.7	25.6	1.38	19.06	.002[a]	57.4	27.7	2.11	39.90	.0002[a]
Reexperiencing	19.3	9.8	10.6	8.0	0.94	8.82	.016[a]	12.6	8.9	1.30	15.32	.0045[a]
Avoidance/Numbing	36.3	6.2	27.8	12.4	0.92	8.42	.02[a]	27.6	12.4	0.95	8.05	.02[a]
Hyperarousal	27.3	5.0	18.3	9.4	1.28	16.49	.003[a]	17.3	9.1	2.10	39.74	.0002[a]
DTS total	99.3	20.4	71.3	42.5	0.95	9.00	.015[a]	64.2	44.7	1.17	12.33	.008[a]
Reexperiencing	25.0	10.0	20.3	14.3	0.50	2.54	NS	15.3	13.8	0.94	7.90	.02[b]
Avoidance/Numbing	40.5	9.5	28.8	16.9	0.86	7.35	.02[a]	28.3	19.5	0.88	6.91	.03[a]
Hyperarousal	34.0	5.1	22.2	12.6	1.30	16.88	.003[a]	20.6	12.4	1.40	17.66	.003[a]
PSQI	13.2	2.8	7.7	4.3	1.44	20.65	.001[a]	6.7	5.2	1.31	15.35	.004[a]
Sleep/night, h	4.4	0.9	6.8	1.4	1.73	30.08	.0004[c]	6.7	1.6	1.27	14.47	.005[c]
Depression												
HAM-D	25.6	9.1	17.0	10.1	1.11	12.35	.007[a]	14.0	10.1	1.89	32.12	.0005[a]
BDI	24.6	9.6	23.0	13.1	0.19	0.35	NS	21.6	14.6	0.48	2.06	NS

*BDI = Beck Depression Inventory, CAPS = Clinician Administered PTSD Scale, DTS = Davidson Trauma Scale, HAM-D = Hamilton Rating Scale for Depression, PSQI = Pittsburgh Sleep Quality Index, PTSD = posttraumatic stress disorder.
[a]Baseline value significantly greater than week 12 and week 16 values.
[b]Baseline value significantly greater than week 16 value.
[c]Baseline value significantly less than week 12 and week 16 values.

PTSD or a physical disorder; 2 were seeking service connection, and 1 was not. The mean GAF score for the patients was 55, with a range of 45 (serious symptoms) to 65 (moderate symptoms). Three were employed full-time; 1 was employed part-time; the remaining 6 were unemployed. Mean self-reported onset of PTSD symptoms was 18 years previously, with a range of 5 to 25 years. The medication was well tolerated; only minor side effects, including dry mouth, headache, tinnitus, and frequent urination, were reported at various times during the study.

All patients were treated solely with nefazodone by one of the authors (M.A.H.). This was an open-label study, i.e., patients were aware of the name of the medication prescribed. During the course of this protocol, patients did not receive any new additional treatments, including other psychotropic medications, with the 1 exception that, in week 10, 1 subject began individual psychotherapy. One subject was in ongoing individual psychotherapy (12 months), and 4 of the 10 had been previously treated with pharmacotherapy for their PTSD symptoms with minimal or unsustained response. Six were new patients to the clinic, and mean enrollment in the clinic for the remaining 4 prior to study participation was 3 years.

Symptom Measures Across Treatment

All patients were considered to be responders at posttreatment as measured by the CGI-I (i.e., much improved or very much improved). Repeated analyses of variance (ANOVAs) with post hoc comparisons were performed to determine the significance of changes associated with treatment. Given the limited power inherent in a pilot study of 10 subjects, effect size and assessments of the clinical significance of change are considered more salient than tests of statistical significance. Effect size rating and results of ANOVAs for symptom measures are presented in Table 1.

All symptom rating scale scores improved from the baseline to the posttreatment (week 12) visits. Except for BDI scores and PTSD reexperiencing symptoms for the DTS, all comparisons from pretreatment to posttreatment (week 12) and follow-up (week 16) were statistically significant. Effect sizes for all significantly changed symptoms were moderate to large.[35] PTSD reexperiencing symptoms for the DTS improved significantly by follow-up (week 16). Effect sizes were highest for PTSD hyperarousal symptoms (for both CAPS and DTS), HAM-D scores, and PSQI scores. Although conclusions cannot be made from a single item from multiple-item rating scales, it was noted that on both the CAPS and DTS items, mean anger intensity and frequency decreased over the treatment (CAPS, 38%; DTS, 26%) and follow-up periods (CAPS, 62%; DTS, 45%).

DISCUSSION

Our data showed that nefazodone treatment may be effective in reducing many symptoms of chronic PTSD, including sleep disorder symptoms. Symptoms were rated as improved on the CGI-I, DTS, CAPS, PSQI, and HAM-D, and moderate-to-large effect sizes were observed for each significant measure.[35] Across the 3 symptom clusters, effect sizes were largest for PTSD hyperarousal symptoms. Depression as measured by the self-report BDI did not improve. Treatment gains were maintained at follow-up. A disturbed sleep/dream cycle

plays a prominent role in PTSD, and nefazodone's ability to increase sleep and improve sleep quality may be important to our findings of improved PTSD symptoms.

Our results regarding improvement in PTSD symptoms and anger are consistent with other open trials using trazodone,[23] fluoxetine,[12,36] and fluvoxamine.[13] The magnitude of reduction (30%–50%) in symptoms is also similar to[12,13] or greater than that found in other open trials,[8,23] suggesting that although nefazodone will not likely result in full remission of PTSD symptoms in this chronically affected population, it may provide significant partial relief from some of the symptoms of PTSD, particularly sleep and anger. Furthermore, nefazodone may prove useful as adjunctive treatment in combination with other medication or as a second, complementary antidepressant. The magnitude of symptom improvement detected in this study is higher than placebo rates of response in controlled trials (5%–10%),[8,37] and the improvement rate of those identified as responders (100%) was higher than that of those treated with placebo (17%).[38] Notably, improvements associated with this open trial were observed in a population that has been identified as particularly refractory to treatment.[37] Because of the small number of cases, the findings of this nefazodone trial should be confirmed in a double-blind, placebo-controlled trial.

Depression was not improved as measured by the BDI, but was significantly improved as measured by the clinician rating (i.e., HAM-D). These differential findings may be due to 2 different methods of measurement of depression. For example, a lack of improvement as measured by the BDI is consistent with our previous work with trazodone.[23] It may be that the HAM-D ratings are more sensitive to clinical changes than the BDI, or the difference may be due to clinician versus patient perceptions and possible biases.

Anger ratings were greatly improved (up to 62%) over the course of the study. However, anger changes were measured by only 1 item from the CAPS and the DTS. Given the importance of chronic anger, hostility, and interpersonal violence in this population,[39,40] this may be an important target symptom in future trials and deserves more reliable and valid measurement of possible change. Since effective psychopharmacologic treatment interventions for combat veterans with chronic PTSD have not yet been identified, safe and cost-effective avenues for symptom relief and partial improvement, such as nefazodone, merit continued evaluation.

Drug names: alprazolam (Xanax), carbamazepine (Tegretol and others), fluoxetine (Prozac), fluvoxamine (Luvox), nefazodone (Serzone), propranolol (Inderal and others), sertraline (Zoloft), trazodone (Desyrel and others), valproic acid (Depakene and others).

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