Nefazodone in Patients With Treatment-Refractory Posttraumatic Stress Disorder

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Background: Posttraumatic stress disorder (PTSD) is a highly prevalent and often chronic disorder among combat veterans, persisting in as many as 15% of Vietnam veterans for at least 20 years. Treatment response in veterans with combat-related PTSD has been disappointing. Although anxiolytics, anticonvulsants, antipsychotics, and antidepressants have been tried, none has been consistently associated with improvement in all primary symptom domains (i.e., intrusive recollections, avoidance/numbing, and hyperarousal). This open-label study evaluated the use of nefazodone in a group of Vietnam veterans with chronic, treatment-refractory symptoms of PTSD.

Method: Male outpatients with DSM-IV PTSD who had failed a minimum of 3 previous medication trials were eligible for the study. Nineteen Vietnam combat veterans entered the study and were treated with nefazodone, 100–600 mg/day, for 12 weeks. PTSD symptoms, anxiety, depression, sleep, sexual functioning, and adverse events were assessed weekly.

Results: Severity of depression lessened, as did PTSD symptoms of intrusive recollections, avoidance, and hyperarousal. Depressive symptom severity as measured by the Beck Depression Inventory decreased by a mean of 30%. Similarly, there was an overall drop in the intensity of PTSD symptoms as measured by the Clinician Administered PTSD Scale of 32% with a 26% improvement for symptoms of intrusion, 33% for avoidance, and 28% for arousal. In addition, improvements in sleep and sexual functioning were reported. The mean daily dose of nefazodone after 12 weeks was 430 mg (range, 200–600 mg/day). The most frequently reported side effects were headaches (53%), dry mouth (42%), and diarrhea (42%), but side effects tended to be mild and transient.

Conclusion: In this group of Vietnam veterans with chronic treatment-refractory PTSD and multiple comorbid Axis I psychiatric disorders, nefazodone was well tolerated and effective. Larger, controlled studies are warranted.

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Controlled studies of the efficacy of antidepressant medications for the treatment of posttraumatic stress disorder (PTSD) have not yet revealed a clear-cut treatment of choice. The best-studied class of medications has been the tricyclic antidepressants (TCAs). In the first controlled study of the TCAs, Reist et al.[1] found desipramine no more effective than placebo in 18 veterans in a 4-week crossover trial. In another study, Davidson et al.[2] reported modest benefits with amitriptyline in World War II and Vietnam combat veterans, with greatest improvement seen in symptoms of avoidance. In a third trial, Kosten et al.[3] compared imipramine with phenelzine in Vietnam combat veterans and found both superior to placebo, with phenelzine having some advantages over imipramine. However, a small and brief crossover study[4] of 13 patients with PTSD found no difference between phenelzine and placebo.

In the only controlled study of selective serotonin reuptake inhibitors (SSRIs) for PTSD, van der Kolk et al.[5] found fluoxetine more effective than placebo in 33 non–combat-related PTSD patients, but not in 31 war veterans with combat-related PTSD. In that trial, more benefit was found in hyperarousal and numbing symptom clusters than in reexperiencing or avoidance symptoms.[5] Several noncontrolled studies of other SSRIs, including fluvoxamine,[6,7] sertraline,[8,9] and paroxetine,[10] suggest the potential usefulness of this class of agents for not only the core symptoms of PTSD, but also for symptoms of comorbid depression, anxiety, and substance abuse. Although the results of these preliminary studies are promising, they are limited by small sample sizes and the open-label, nonblinded study designs.

Several other classes of medications also have been studied. Two controlled studies with benzodiazepines, for example, were generally negative.[11,12] In the first, a 5-week crossover trial with alprazolam in a mixed sample of veterans and civilians, Braun et al.[11] reported some reduction in anxiety, but no significant benefit in core symptoms of PTSD for patients who received alprazolam. In a small prospective trial[12] of alprazolam or clonazepam versus placebo in civilian trauma survivors who were treated shortly after the trauma, neither benzodiazepine was found to benefit the course of illness weeks to months later. Kaplan et al.[13] reported no benefits of treatment with inosital compared with placebo in a small, 4-week trial of civilians with PTSD. A number of noncontrolled, generally small studies have suggested a possible role for anticonvulsants,[14,15] trazodone,[16] buspirone,[17] lithium,[18] mirtazapine,[19] and bupropion[20] for some of the symptom clusters and/or comorbid conditions associated with PTSD, but none of these trials have demonstrated consistent efficacy across all major symptom clusters of PTSD. A recent report[21] from 6 open-label trials with nefazodone involving both civilian and combat veterans suggested possible efficacy across a broad spectrum of PTSD symptoms with youth, female gender, and noncombat trauma all predicting positive response.

From the above, it is no surprise that many patients with PTSD, especially combat veterans,[5] have chronic symptomatology despite relatively aggressive attempts at treatment. These patients present vexing therapeutic challenges to even the most gifted clinicians and treatment programs. The present study was undertaken to assess whether nefazodone, a serotonin-2 (5-HT_2) antagonist and modest inhibitor of serotonin and norepinephrine reuptake, would benefit Vietnam combat veterans who had not derived adequate benefits from other medications.

METHOD

Subjects

The subjects were 19 community-residing, male Vietnam veterans who were referred by the Vietnam Veterans of San Diego Center or San Diego Veterans Affairs Medical Center PTSD Clinic for this study. Subjects were included if they: (1) met DSM-IV criteria for chronic PTSD; (2) had failed at least 3 previous full trials of antidepressant treatment (defined as trials lasting 1 month or longer with no response or intolerable side effects), at least 1 of which was an SSRI; (3) were not presently psychotic; and (4) did not meet DSM-IV criteria for current substance abuse or dependence. Subjects who had been previously treated with nefazodone were excluded, as were subjects who could not discontinue the use of other psychotropic medication for at least 1 week. Patients were required to be off fluoxetine therapy for at least 4 weeks, other antidepressants for 1 week, and hypnotic/sedative medications for 3 days before beginning treatment. Subjects with prominent suicidal ideation also were excluded. Written and verbal informed consents were obtained at the time of the initial screening interview.

General Study Design

An open-label clinical trial was conducted with Vietnam veterans carrying primary diagnoses of combat-related PTSD. During weeks 0 to 2, patients were interviewed for DSM-IV diagnoses (using the Mini-International Neuropsychiatric Interview [MINI], Clinician Rated[22]) and other inclusion/exclusion criteria and were washed out of all psychotropic medications. Of the 32 patients who were referred and screened, 12 were not included. Ten of these men did not have documented evidence of 3 treatment failures, and 2 were using substances excluded by the study protocol. One patient dropped out during the washout period because of symptom exacerbation. Thus, 19 patients entered the treatment phase of the study.

The 19 subjects satisfying all study inclusion criteria were started with nefazodone, 100 mg q.h.s., at week 2. If tolerated, the dose of nefazodone was increased to 300 mg by the beginning of week 3. After that, a flexible dosing strategy was utilized with the goal of maximizing efficacy while minimizing side effects. Medications were prescribed to be taken twice daily. Compliance was measured by verbal report and pill count check. Patients were seen weekly for 12 weeks. Concomitant therapy was minimized. Patients who were already in psychotherapy were allowed to continue, but newly initiated psychotherapy was not allowed. Concurrent psychotropic medications were not allowed. At the conclusion of the 12-week treatment, patients were referred to appropriate clinicians at the Veterans Affairs Medical Center, where their medication could be continued.

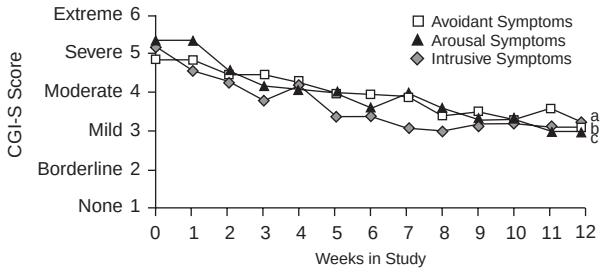
Measures

For diagnosis, all patients were administered the clinician-rated MINI.[22] The primary measure of PTSD frequency and intensity was the Clinician Administered PTSD Scale (CAPS), administered at baseline and at the end of the study.[23] In addition, PTSD was assessed further by the Clinical Global Impressions-Severity and -Improvement scales for PTSD (CGI-S and CGI-I), administered weekly. Both global measures use a 6-point scale to assess 3 symptom domains of PTSD: avoidance, intrusive symptoms, and hyperarousal. Depression was measured at each visit by the self-rated Beck Depression Inventory (BDI)[24] and at baseline and at end of the study by the clinician-rated 17-item Hamilton Rating Scale for Depression (HAM-D),[25] and anxiety was measured at baseline and endpoint by the Sheehan Patient Rated Anxiety Scale (SPRAS).[26] At the beginning and end of the study, sleep was measured with the Pittsburgh Sleep Quality Inventory (PSQI),[27] and

Table 1. Side Effects

Effect	N	%
Headaches	10	53
Dry mouth	8	42
Diarrhea	8	42
Tired/drowsy	7	37
Memory problems	7	37
Dizziness	6	32
Blurred vision	6	32
Confusion	6	32
Difficulty concentrating	4	21
Lightheadedness	3	16
Indigestion	3	16
Constipation	3	16
Frequent urination	3	16
Shortness of breath	2	11
Hypotension	2	11
Tremor	2	11
Nausea	2	11

Figure 1. Posttraumatic Stress Disorder (PTSD) Symptom Severity Over Time Measured by the Clinical Global Impressions-Severity Scale (CGI-S)



[a]Intrusive symptoms: F = 9.81, df = 14, p < .001 vs. baseline.
[b]Avoidant symptoms: F = 5.14, df = 14, p < .001 vs. baseline.
[c]Arousal symptoms: F = 12.38, df = 14, p < .001 vs. baseline.

sexual functioning was measured by a series of self-rated Likert scales (available on request) measuring libido, excitement, ejaculation, orgasm, and satisfaction on a scale of 0 (much less than usual) to 7 (much more than usual). Reports of side effects were elicited by asking patients at each follow-up visit whether they had experienced any side effects, new symptoms, or problems since the last visit. Symptoms were counted as side effects independent of severity, the need for treatment, or clinician's judgment regarding the likelihood of being related to treatment. No baseline measure of potential adverse experiences was taken before treatment.

Analysis

Pretreatment and posttreatment scores were compared by repeated measures analysis of variance (ANOVA) or paired 2-tailed t tests. Separate analyses were conducted for the intent-to-treat sample (N = 19) and the completer sample (N = 15).

RESULTS

Nineteen treatment-refractory patients entered the study. The mean number of years of formal education was 15, with a range of 9 to 20 years. Twenty-six percent of the patients (N = 5) were presently married, 53% (N = 10) had had 2 or more divorces, and 84% (N = 16) were unemployed. The most common comorbid conditions were major depression (84%; N = 16), agoraphobia (79%; N = 15), current or past dysthymia (68%; N = 13), panic disorder (58%; N = 11), generalized anxiety disorder (26%; N = 5), and social phobia (26%; N = 5). The mean number of concurrent Axis I diagnoses was 4 (range, 0–6).

Compliance with the study protocol was good: 15 (79%) of 19 patients completed the 12-week trial. Three patients dropped out of the study at weeks 4, 5, and 8 because of a combination of lack of efficacy and irritability, and 1 patient discontinued from the study at week 9 owing to side effects (hypotension/dizziness). No statistically significant demographic differences were found between the patients who discontinued the study early and those who completed the trial. The 15 patients who completed the study were followed for 12 weeks. The mean dose of nefazodone at the last visit was 424 mg/day for the intent-to-treat sample and 430 mg/day (range, 200–600 mg) for the completer sample. Only 2 patients reached the maximum dose of 600 mg/day at the end of the study.

Side effects were reported by all nineteen subjects (Table 1), but tended to be mild and transient.

CGI-S Scores

A repeated measures ANOVA comparison of severity of PTSD as captured by weekly CGI-S ratings revealed significant improvement across all 3 subscales of intrusive, avoidant, and hyperarousal PTSD symptoms. After treatment with nefazodone, the severity of intrusive recollections declined significantly from a mean of 5.20 at baseline to a mean of 3.10 at endpoint (F = 9.81, df = 14, p < .001). The severity of avoidance behaviors also declined significantly from a mean of 4.9 to 3.1 (F = 5.14, df = 14, p < .001), and severity of hyperarousal symptoms dropped from a mean rating of 5.4 to 3.0 (F = 12.38, df = 14, p < .001). As demonstrated in Figure 1, overall severity of PTSD symptoms rapidly diminished from the severe/extreme to the moderate range during the first month of treatment (weeks 1–4); the symptom severity continued to steadily decline to the mild range over the remaining 2 months of treatment (weeks 4–12).

CAPS Frequency and Intensity Scores

The CAPS frequency mean ± SD score decreased from 42.1 ± 11.1 at baseline to 29.3 ± 11.5 at endpoint (t = 5.55, df = 17, p < .001) for a 31% reduction in symptoms. Twenty-two percent of patients experienced an improve-

Figure 2. PTSD Symptoms Measured by the Clinician Administered PTSD Scale (CAPS), Intensity Subscale

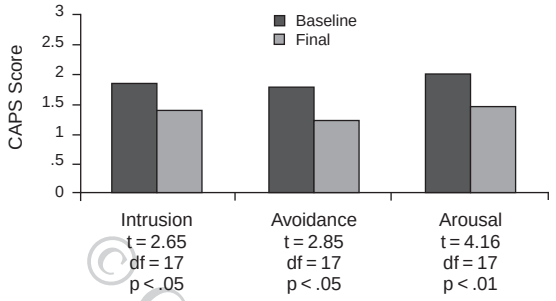
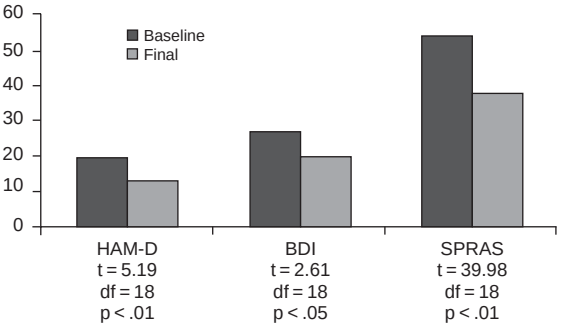


Figure 3. Changes in Depression and Anxiety From Baseline to Final Rating[a]



[a]Abbreviations: BDI = Beck Depression Inventory, HAM-D = 17-item Hamilton Rating Scale for Depression, SPRAS = Sheehan Patient Rated Anxiety Scale.

ment of 50% in CAPS frequency score. The CAPS intensity mean ± SD score decreased from 33.7 ± 9.7 at baseline to 23.0 ± 10.3 at endpoint ($t = 5.1$, $df = 17$, $p < .001$) for a 32% reduction in symptoms. Thirty-three percent of patients experienced an improvement of ≥ 50% in CAPS intensity score. All CAPS subscores of the frequency and intensity of PTSD symptoms declined from baseline to endpoint. For the intent-to-treat sample, the decline was statistically significant for the frequency of intrusion ($t = 3.36$, $df = 17$, $p < .05$; 26% decrease), avoidance ($t = 2.5$, $df = 17$, $p < .05$; 33% decrease), and arousal ($t = 2.65$, $df = 17$, $p < .05$; 28% decrease) symptom clusters, and for the intensity of intrusion ($t = 2.65$, $df = 17$, $p < .05$; 26% decrease), avoidance ($t = 2.85$, $df = 17$, $p < .05$; 33% decrease), and arousal ($t = 4.16$, $df = 17$, $p < .01$; 28% decrease) symptom clusters. Since the results of the frequency and intensity analyses are so similar, Figure 2 illustrates only the CAPS intensity scores from baseline to endpoint.

Depression and Anxiety Scores (Figure 3)

Paired t test comparisons of HAM-D scores before and after treatment with nefazodone revealed significant amelioration of the severity of depressive symptoms. The mean HAM-D scores dropped by 37% from baseline (HAM-D score = 19) to endpoint (HAM-D score = 12; $t = 5.19$, $df = 18$, $p < .01$). Twenty-eight percent of patients reported at least 50% reduction in HAM-D scores. Similarly, patient self-ratings on the BDI demonstrated a significant reduction ($t = 2.61$, $df = 18$, $p < .05$; 30% decrease) in depressive symptoms similar to that of the physician-rated HAM-D.

Severity of anxiety symptoms as measured by the SPRAS also showed significant improvement, declining from a mean total of 54 to 38 ($t = 39.98$, $df = 18$, $p < .01$). Thirty-nine percent of patients reported at least 50% reduction in SPRAS scores.

Sleep Variables

One patient was an outlier on the sleep variables due to excessive somnolence at baseline. He reported sleeping more than 12 hours daily at baseline and rated his sleep as "very bad" with "many" nightmares, and he "always" felt groggy during the day. At week 12, he reported sleeping 8 to 8 1/2 hours daily, and he rated his sleep as "very good." His sleep data were not considered for the following analyses.

Table 2. Other Domains[a]

Domain	Pre-treatment	Post-treatment	Statistic[b]	p Value
Sex past week (from Likert scale, 0–6), N (%)				
More than usual desire (N = 15)	1 (7)	5 (33)	–2.23	< .05
More than usual enjoyment (N = 14)	1 (7)	4 (29)	–1.52	NS
Sleep past week (from PSQI; N = 17)				
Mean hours sleep/night	5	5.9	4.20	< .01
No bad dreams, N (%)	2 (12)	6 (36)	2.49	< .05
"Good" quality of sleep, N (%)	2 (12)	10 (59)	3.31	< .01
Being able to fall asleep most nights, N (%)	1 (6)	7 (41)	3.07	< .01
Waking up in the middle of the night, N (%)	17 (100)	11 (65)	2.72	< .05
Social/interpersonal past 2 weeks, N (%)				
Interested in dating (N = 12)	4 (33)	8 (67)	1.88	.06

[a]Abbreviation: PSQI = Pittsburgh Sleep Quality Inventory.
[b]t Test or Wilcoxon test.

Total self-reported hours of sleep per night by the other patients increased by approximately 1 hour from a mean of 5.0 hours per night to a mean of 5.9 hours per night over the course of the study ($t = 4.20$, $df = 15$, $p < .01$). As Table 2 shows, patients reported improvement in being able to fall asleep ($t = 3.07$, $df = 15$, $p < .01$). In addition, the frequency of waking up in the middle of the night or early morning diminished ($t = 2.72$, $df = 15$, $p < .05$), and patients reported having fewer bad dreams at the end of the study compared with baseline ($t = 2.49$, $df = 15$, $p < .05$). Finally, self-reported assessment of overall quality of sleep

before and after treatment demonstrated a significant improvement ($t = 3.31$, $df = 15$, $p < .01$) after treatment with nefazodone.

Sexual and Social Functioning

Because 15 men in this study were unmarried, most tended to be socially isolated, and few had ongoing sexual partners, it was difficult to measure changes in sexual function over only 3 months of treatment. However, most subjects were able to provide self-rated assessments of their level of sexual desire and enjoyment of sex or masturbation. Despite the methodological limitations, the data suggest an increase in sexual desire and arousal after treatment (see Table 2). The completer sample showed a statistically significant improvement in sexual desire ($t = –2.23$, $df = 14$, $p < .05$). Both the intent-to-treat and completer samples were more likely to achieve arousal after treatment: ($t = –2.13$, $df = 19$, $p < .05$) for the intent-to-treat sample, ($t = –2.17$, $df = 13$, $p < .05$) for the completer sample. There was a statistical trend toward an increased interest in dating from baseline to end of study ($t = 1.88$, $df = 11$, $p = .06$).

DISCUSSION

Nefazodone was well tolerated and effective in this population of 19 male Vietnam veterans. Although more side effects were noted than in other populations we have treated with nefazodone, the side effects tended to be mild and transient, did not interfere with achieving therapeutic doses of nefazodone relatively early in treatment, and led to only 1 dropout. The 1 dropout had a history of dizziness and hypotension, reexperienced both shortly after beginning treatment, and dropped out after 9 weeks of treatment. Although his blood pressure ran low, there were no clinically significant orthostatic changes. Other common side effects, such as headaches, dry mouth, diarrhea, somnolence, and memory problems, were qualitatively similar to what we have seen in other patients treated with nefazodone. This study was not a placebo-controlled trial; thus, we were not able to identify treatment-emergent adverse events with certainty. It should also be noted that, despite our explicit instructions, at least 3 of the patients took all of their medications before bedtime. In each case, they justified their protocol violation by stating they were trying to manage their insomnia and nightmares. Uniformly, they felt the strategy was beneficial, and they continued to derive benefit in all symptom domains during daytime. On the basis of those 3 patients, we ended up prescribing nefazodone in doses between 300 to 600 mg/day exclusively at bedtime for 3 other individuals. This dosing strategy appeared effective and well tolerated for these men.

Notwithstanding the chronicity and treatment refractoriness of the population, nefazodone was effective for treating the core PTSD symptoms of reexperiencing, avoidance and numbing, and hyperarousal. In particular, symptoms of hyperarousal appeared to respond most quickly, with the mean symptom severity range going from "severe" to "moderate" intensity by weeks 2 to 3 and to "mild" severity by 6 to 8 weeks. Gradual improvement of all symptom clusters continued throughout the 12 weeks of active treatment. It is not unlikely that additional improvement over time is related to the dose escalation as the study progressed. By the end of 12 weeks, all symptom clusters were in the mild range, suggesting both significant improvements from baseline as well as continued residual symptomatology and room for further improvement. Twelve weeks may not be an adequate trial, certainly not for maximal benefits. Not unexpectedly, nefazodone was effective in treating symptoms of anxiety and depression as well. Since many previous studies in U.S. veterans have not revealed such considerable improvement across all symptom domains of PTSD, anxiety, and depression,[28] we view these results as promising and worthy of further exploration through controlled trials.

In addition to symptomatic improvement, quality of life also was enhanced during this brief 12-week trial. Sex was more enjoyable than it had been and sleep more restful. Previous studies in other populations have also found improvement in sexual functioning[29] and sleep efficiency[30] associated with nefazodone treatment. More germane to this study, Mellman[31] has reported improved quality of both sleep and dreams in patients with PTSD after 6 weeks of treatment with nefazodone. Since the present study included such a highly impaired group of individuals with poor education, multiple divorces, multiple comorbidity, and prolonged disability, to even begin to improve quality of life during the few short weeks of this study was a formidable and rewarding task. Controlled trials with longer periods of follow-up, larger samples, and more sensitive ratings of quality of life would be a reasonable next step in evaluating the benefits of nefazodone in this population.

We were somewhat surprised by the low dropout rate. We attributed much of this to the care, attention, and support provided by the research staff, emphasizing the importance of nonpharmacologic factors in overall effectiveness of any treatment approach. Patients also indicated that the sleep-enhancing properties of the treatment were an important aspect of their overall satisfaction with the study. Almost all the patients (14/15) indicated their desire to remain on nefazodone treatment after the conclusion of the study, but we did not continue to systematically follow patients after the 12-week treatment period.

In summary, nefazodone appeared to be a well-tolerated, safe, and effective treatment of Vietnam combat veterans with chronic, treatment-refractory PTSD. Its benefits were seen across 3 major clinical domains of PTSD—reexperiencing, numbing and avoidance, and hyper-

arousal—as well as in symptoms of depression and anxiety. Improved quality of sleep and sexual satisfaction were also found. Further controlled trials are warranted.

Drug names: alprazolam (Xanax and others), amitriptyline (Elavil and others), bupropion (Wellbutrin), buspirone (BuSpar), clonazepam (Klonopin and others), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), mirtazapine (Remeron), nefazodone (Serzone), paroxetine (Paxil), phenelzine (Nardil), sertraline (Zoloft), trazodone (Desyrel and others).

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