

Nefazodone Versus Sertraline in Treatment of Posttraumatic Stress Disorder

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ABSTRACT:

NEFAZODONE VERSUS SERTRALINE IN TREATMENT OF POSTTRAUMATIC STRESS DISORDER

Objective: Nefazodone is an antidepressant that has a dual effect on serotonergic transmission by acting as both a reuptake inhibitor presynaptically and an antagonist at 5-HT_{2A} receptor postsynaptically. Some authors have suggested that the 5-HT_{2A} receptor may be involved in the pathophysiology of posttraumatic stress disorder (PTSD). In this study, the efficacy of nefazodone in treatment of PTSD was investigated in comparison to the efficacy of sertraline.

Methods: Subjects were randomly assigned to two treatment groups, nefazodone or sertraline group. Sixty subjects were recruited with 30 subjects in each treatment group. PTSD patients were diagnosed by using the Structured Clinical Interview for DSM-IV (SCID-1) and nonstructured psychiatric interview. Measurements have been made every month for a five-month period with six assessment points including the baseline. Primary outcome measures consisted of the Posttraumatic Stress Diagnostic Scale (PDS), the eight-item Treatment-outcome Posttraumatic Stress Disorder Scale (TOP-8), Clinical Global Impression Scale (CGI) ratings.

Results: The subjects in both of these groups had significantly improved. There were significant differences between initial and endpoint TOP-8 and CGI scores ($p < 0.001$).

Conclusions: The results of the current study suggest that nefazodone is significantly effective as sertraline in treatment of PTSD.

Key Words: Posttraumatic stress disorder, nefazodone, sertraline, pharmacotherapy

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INTRODUCTION

Posttraumatic Stress Disorder (PTSD) is a psychiatric illness with a lifetime prevalence (range of 5% to 12%) reported to be in most prevalent of all psychiatric disorders (1). PTSD is also associated with significant functional and psychosocial disability (2,3). Its treatment may sometimes be quite difficult, as there is no identified golden standard pharmacological agent, meanwhile there are some efforts for clinical consensus about it. In 1999, some experts of PTSD published a consensus guideline (4). They suggested that if the selective serotonin reuptake inhibitors (SSRI) did not work or caused side effects that required a switch to a different class of medication, nefazodone would be the next choice. This clinical judgement requires further research regarding the efficacy of nefazodone in the treatment of PTSD. Currently, there are a few open-label nefazodone trials in treatment of PTSD (5,6,7). Hidalgo et al (1999)

made a meta-analysis with six open label studies involving civilians and combat veterans who suffer from PTSD. One hundred five outpatients with chronic PTSD were treated with nefazodone. Nefazodone showed a broad spectrum of action on PTSD symptoms, in the analysis. But these studies were not controlled, the samples were not homogeneous and different scales were used (8).

The present study was designed to determine the efficacy of nefazodone versus sertraline which is FDA approved (1999) pharmacological treatment agent of PTSD (9,10), in a homogeneous subject population that were exposed to the same type of trauma (earthquake).

METHODS

Subjects:

Marmara Earthquake hit Turkey, on August 17th,

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1999. Approximately 18,000 people died, 45,000 others were injured. Izmit was the area that was severely hit by this earthquake. Subjects were recruited from an out-patient trauma clinic based in Izmit, Izmit Rehabilitation Center, (IREM). The patient population of IREM mainly consisted of PTSD patients. Patients that had lost part of their extremities were treated in collaboration with the physical rehabilitation section of the same center. IREM works as a non-profit organization sponsored by the Mother and Child Education Foundation (AÇEV) and American Project Hope. Subjects were randomly assigned to one of the two treatment groups, nefazodone or sertraline. Subjects who had a history of alcohol or drug abuse, neurological disorder, current organic mental disorder and who are under psychiatric medication less than 2 weeks before the study were all excluded. All subjects gave written informed consent before participating in the study. There were 30 patients in each treatment group. As 6 patients dropped out of the nefazodone group, sample size was 54, with 30 subjects in sertraline group and 24 subjects in nefazodone group.

Procedure:

Diagnoses of PTSD was made by nonstructured clinical interview by a psychiatrist and then independently by a psychologist using SCID-1. Subjects were evaluated and rated once in a month, for a period of six months. Instruments used were The Posttraumatic Stress Diagnostic Scale (PDS) (11), The eight-item Treatment-outcome Post-traumatic Stress Disorder Scale (TOP-8) (12), The Clinical Global Impression Scale (CGI) (13). Subjects were treated with one of these drugs, at flexible doses according to their clinical status. The mean dose of sertraline was 68.33 ± 21.70 mg/day, with a range between 50-100 mg/day. The mean dose of nefazodone was 332.35 ± 63.5 mg/day, range being 200-400 mg/day.

Statistical Analysis:

The results were analyzed by using SPSS 10.0.5. Statistical significance of differences between interval variables was determined using the Student's t-test and chi-square test for other comparisons. Paired-samples t-test was used for dependent variables. Significance was indicated for $p < 0.05$.

RESULTS

The mean age of the subjects was 37.7 ± 11.49 years in the sertraline group and 46.13 ± 8.21 years in the nefazodone group. The degree of education ($p = 0.079$), the marital status ($p = 0.077$), the occupational status ($p = 0.157$), familial psychiatric background ($p = 0.462$), taking psychological help after trauma of both groups ($p = 0.454$) were similar; the dif-

ferences between two groups being statistically insignificant. Psychiatric history prior to trauma ($p = 0.030$), financial loss related to trauma ($p = 0.017$), severity of trauma ($p = 0.021$), were significantly more frequent in sertraline group. There were 20 (66.6%) females and 10 (33.3%) males in sertraline group, 21 (87.5%) females and 3 (12.5%) males in nefazodone group. Comorbidity was high. 40% of sertraline group and 25% of nefazodone group had another psychiatric diagnosis (Table 1).

Table 1. Additional psychiatric diagnosis in the treatment groups

	Sertraline (n=30)		Nefazodone (n=24)	
	n	%	n	%
Total Comorbidity	12	40	6	25
OCD	5	16,8	0	0
MDD	3	10	2	8,33
GAD	1	3,3	2	8,33
Panic Disorder	1	3,3	0	0
Social Phobia	1	3,3	0	0
Specific Phobia	1	3,3	0	0
Conversion Disorder	0	0	2	8,33

OCD:Obsessive-compulsive disorder, MDD:Major depressive disorder
GAD:Generalized anxiety disorder

Mean TOP-8 total scores in the sertraline group was 19.27 ± 3.89 before treatment, 17 ± 3.93 at the end of first month, 13.43 ± 3.64 at the end of the second month, 10.7 ± 3.28 at the end of the third month, 7.7 ± 2.46 at the end of fourth month, 5.23 ± 3.24 at the end of fifth month. Mean TOP-8 total scores in the nefazodone group was 15.75 ± 3.48 before treatment, 13.06 ± 2.9 at the end of first month, 10.41 ± 2.83 at the end of the second month, 7.65 ± 3.02 at the end of third month, 5.94 ± 2.95 at the end of fourth month, 4.35 ± 2.94 at the end of fifth month (Figure 1). Except the last assessment, the difference among these values was statistically significant ($p < 0.005$). But, the significance disappeared at the last assessment ($p = 0.360$).

Mean CGI-severity scores in the sertraline group was 4.73 ± 0.74 before treatment, 4.5 ± 0.78 at the end of first month, 3.77 ± 0.77 at the end of the second month, 3.43 ± 0.68 at the end of the third month, 2.9 ± 0.8 at the end of fourth month, 2.37 ± 0.93 at the end of fifth month. Mean CGI-severity scores in the nefazodone group was 4.38 ± 0.58 before treatment, 4.06 ± 0.56 at the end of first month, 3.47 ± 0.51 at the end of the second month, 3 ± 0.61 at the end of third month, 2.53 ± 0.8 at the end of fourth month, 2.24 ± 0.97 at the end of fifth month (Figure 2). CGI-severity scores of both group was statistically similar, at the beginning and end of the treatment ($p > 0.05$).

Mean CGI-improvement scores in the sertraline group was 3.13 ± 0.78 at the end of first month, 2.7 ± 0.6 at the end of the second month, 2.63 ± 0.89 at the end of the third month, 2.43 ± 0.86 at the end of fourth month, 2.33 ± 0.8 at the end of fifth month.

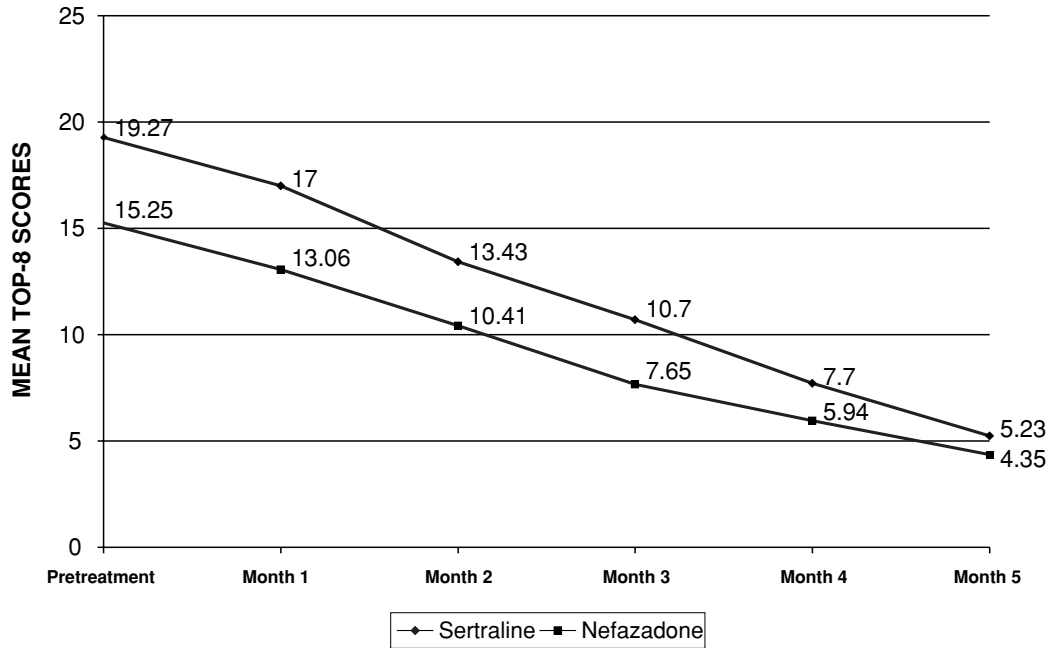


Figure 1. Mean TOP-8 scores of the patients who were treated with sertraline or nefazadone

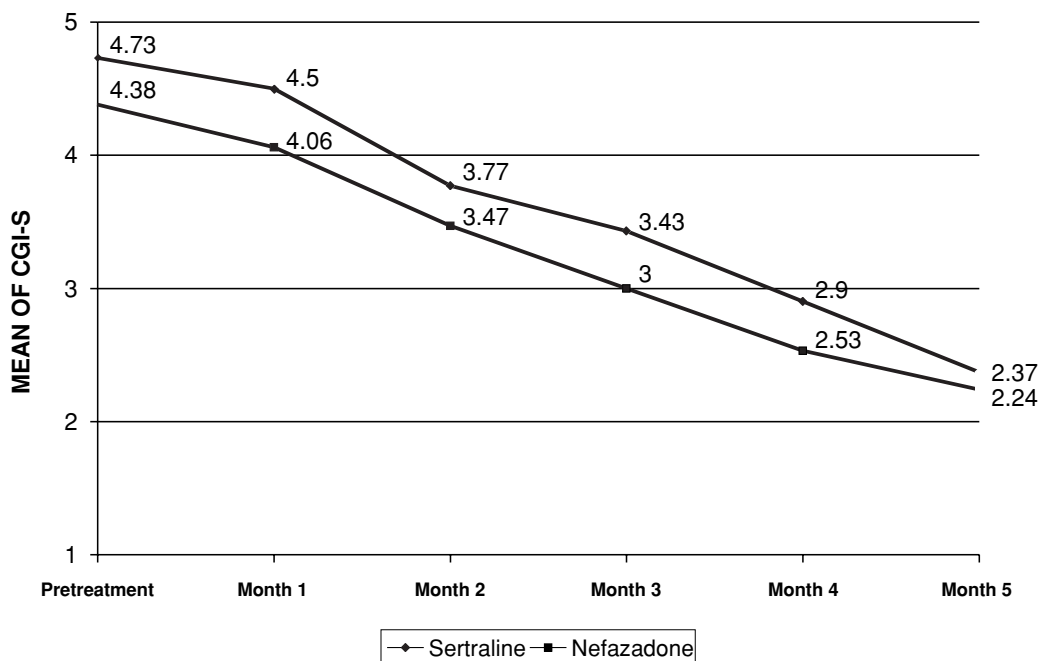


Figure 2. Mean of CGI-severity scores of the patients were treated with sertraline or nefazadone

Mean CGI-improvement scores in the nefazodone group was 3.06 ± 0.66 at the end of first month, 2.71 ± 0.59 at the end of the second month, 2.65 ± 0.7 at the end of third month, 2.71 ± 0.69 at the end of fourth month, 2.41 ± 0.87 at the end of fifth month (Figure 3). The difference among these values was statistically not significant ($p > 0.05$).

Mean CGI-side effect scores in the sertraline group

was 1.87 ± 1.07 at the end of first month, 1.8 ± 1.06 at the end of the second month, 1.53 ± 0.73 at the end of the third month, 1.4 ± 0.67 at the end of fourth month, 1.33 ± 0.55 at the end of fifth month. Mean CGI-side effect scores in the nefazodone group was 2.71 ± 1.21 at the end of first month, 2.53 ± 1.12 at the end of the second month, 2 ± 1 at the end of third month, 1.94 ± 0.9 at the end of fourth month,

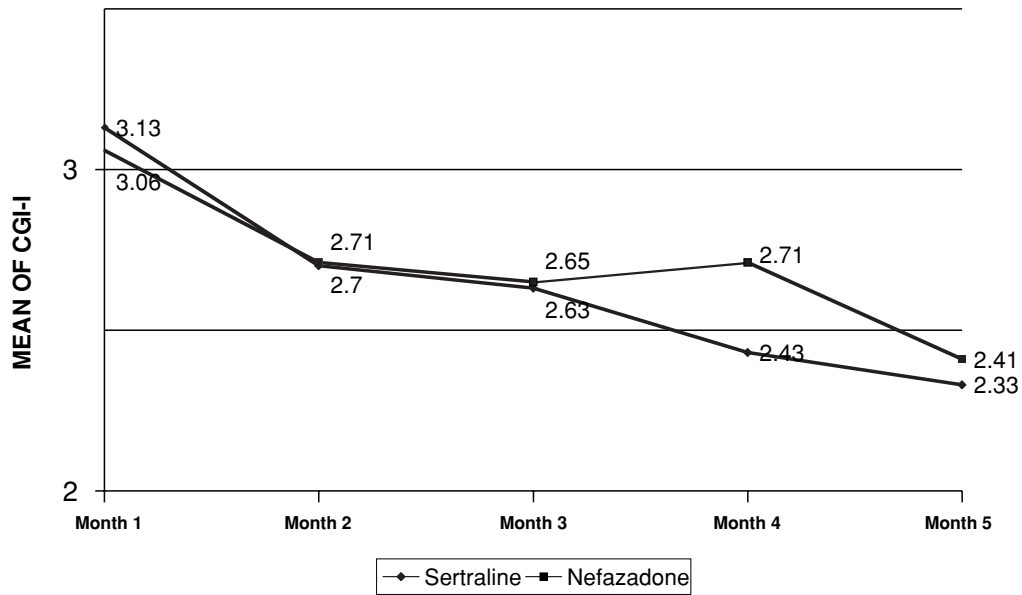


Figure 3. Mean of CGI-improvement scores of patients who were treated with sertraline or nefazodone

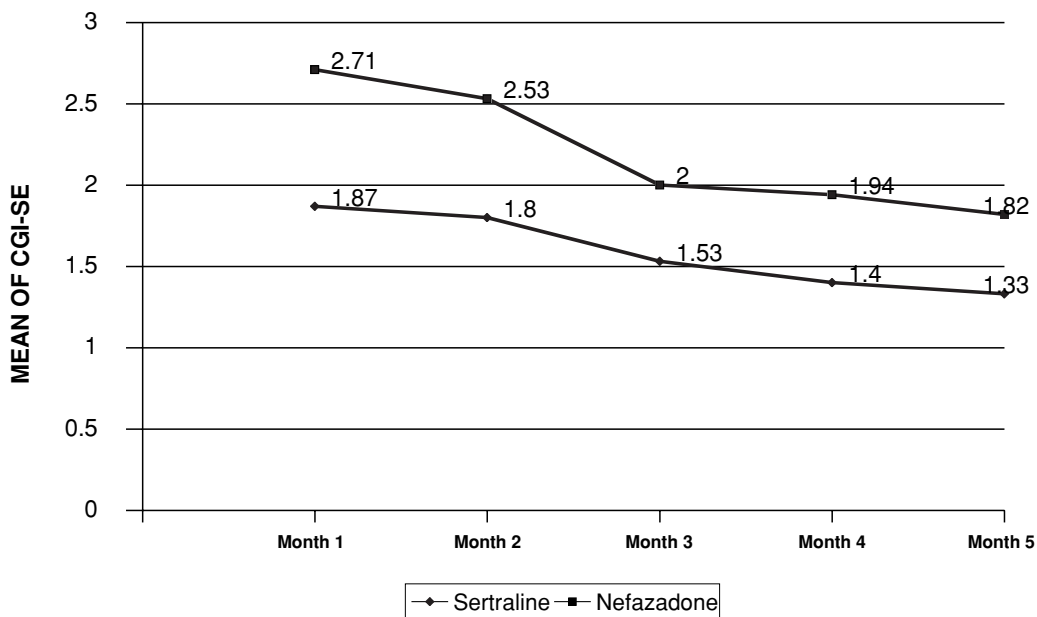


Figure 4. Mean of CGI-side effect scores of patients who were treated with sertraline or nefazodone

1.82±0.73 at the end of fifth month (Figure 4). The overall CGI medication side effect scores were significantly higher for nefazodone ($p < 0.005$), except fourth assessment ($p = 0.073$).

DISCUSSION

The Davidson’s eight-item Treatment Outcome

PTSD scale (TOP-8) examines eight PTSD symptoms that have been shown to respond well to treatment interventions. The eight items belong to all three symptom clusters for PTSD, and have been shown to detect medication/placebo or medication/medication differences better than the other trauma scales (14). TOP-8 total score was significantly higher for sertraline group at the baseline. The mean of TOP-8 total

Table 2. The baseline and endpoint TOP-8 and CGI scores

	TOP-8		CGI-S		CGI-I		CGI-SE	
	First	Last	First	Last	First	Last	First	Last
Sertraline	19.27	5.23	4.73	2.37	3.13	2.33	1.87	1.33
Nefazodon	15.75	4.35	4.38	2.24	3.06	2.41	2.71	1.82

scores of both groups dropped proportionally until the 5th month. But, at the last assessment (between fourth and fifth months), nefazodone group did not improve as much as sertraline group. Further research is needed to find out if sertraline could be more effective in long-term continuation treatment.

The baseline severity score of CGI of both groups were similar (statistically not significant). Severity scores of both groups dropped at similar rates in the five months period and there were significant differences between baseline and endpoint CGI severity scores of both groups.

The CGI-improvement scores of both groups were similar (statistically not significant). Both medications produced similar efficacy, in terms of total improvement of PTSD symptoms.

The CGI-side effect scores were higher for nefazodone group. These scores were statistically significant, except for the fourth assessment. Two patients suffered from dry mouth, three patients had difficulty falling asleep, two patients tachycardia, two had loss of appetite, two had muscular contractions, three had vertigo, three had nausea, two had anxiety, three had day

time sedation in nefazodone group. This study was not designed to assess the side effects of both medications, but it was obvious that nefazodone group. This study is not planned to nefazodone caused more side effects than sertraline in our sample. These side effects may be the reason of six drop-outs from the nefazodone group.

There was a considerable amount of reduction in the final TOP-8 and CGI scores when compared with initial scores for both groups. Differences were statistically very significant ($p < 0.001$) (Table 2). This shows that nefazodone and sertraline were effective in symptom reduction of PTSD.

Major limitation of the current study stems from its design with no double-blinded comparison with placebo. Another limitation of the study is relatively small sample size. The current study should be viewed as a preliminary investigation.

In conclusion, our findings suggests that nefazodone may be a medication of choice for the treatment of PTSD. But, its side effects may restrict usage of this medication in some intolerant patients. Further double-blind placebo controlled comparisons with larger groups is required.

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