Venlafaxine Versus Fluvoxamine in the Treatment of Delusional Depression: A Pilot Double-Blind Controlled Study

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Background: Previous studies have reported the efficacy of selective serotonin reuptake inhibitors as monotherapy in the treatment of delusional depression. The clinical efficacy of venlafaxine, a serotonin-norepinephrine reuptake blocker, has been demonstrated in the treatment of patients with moderate-to-severe depression, but, to date, no evidence is available about its use in depressed patients with psychotic features.

Method: Under double-blind conditions, 28 hospitalized patients who met DSM-IV criteria for major depression, severe with psychotic features, were randomly assigned to receive fluvoxamine or venlafaxine, 300 mg/day, for 6 weeks. Severity was evaluated using the Hamilton Rating Scale for Depression (HAM-D) and the Dimensions of Delusional Experience Rating Scale (DDERS) administered at baseline and every week thereafter. Side effects were also recorded. Clinical response was defined as a reduction of the scores in the 21-item HAM-D to 8 or below and in the DDERS to 0.

Results: At study completion, the response rates were 78.6% (N = 11) and 58.3% (N = 7) for fluvoxamine and venlafaxine, respectively. No significant difference was found between drugs (Fisher exact test, p = .40). Analysis of covariance on HAM-D scores did not reveal a significantly different decrease of depressive symptomatology between the 2 treatment groups (p = .14). Treatment response appeared to be unrelated to the demographic and clinical characteristics recorded. The overall safety profile of both fluvoxamine and venlafaxine was favorable.

Conclusion: The results of this pilot double-blind trial show that fluvoxamine is useful in the treatment of delusional depression and suggest that venlafaxine may also be an effective compound in the treatment of this disorder. The latter finding, although promising, warrants further replication in a larger sample of patients.

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Psychotic depression is a particularly severe form of mood disorder; its prevalence is estimated to be about 20% in patients with depressive episodes and around 0.6% in the general population.[1,2] It has been reported that the rate of delusional depression in hospitalized unipolar depressed patients is approximately 25%.[2]

Patients with delusional depression respond to traditional antidepressant treatments at a lower rate than do nondelusional patients, showing a response rate around 30% to 40%.[3–6] The most efficacious treatments include the combination of antidepressants—tricyclic antidepressants (TCAs) or selective serotonin reuptake inhibitors (SSRIs)—plus neuroleptics or electroconvulsive therapy (ECT).[4–10]

One published double-blind study[11] has compared an SSRI combined with either placebo or neuroleptic with a TCA combined with either placebo or neuroleptic in psychotic depression. In that study, patients were randomly assigned to 4 treatment groups: fluvoxamine plus placebo, fluvoxamine plus haloperidol, desipramine plus placebo, or desipramine plus haloperidol. Fluvoxamine plus placebo showed greater effectiveness than desipramine plus placebo (69% vs. 40%) and was similar to desipramine plus haloperidol (64%).

The effectiveness of certain SSRIs, such as fluvoxamine, sertraline, and paroxetine, has been successfully tested in open and double-blind studies.[12–15] In all these studies, the response rates to SSRIs have appeared to be similar to those obtained by using the combination of antidepressants (SSRIs or TCAs) with antipsychotics or ECT.[4–10] The effectiveness of SSRIs has been accompanied by good safety and tolerability, since the anticholinergic and extrapyramidal side effects usually encountered

using tricyclic and neuroleptic drugs, respectively, have been absent.

According to preclinical studies, venlafaxine is a serotonin-norepinephrine reuptake inhibitor that lacks significant affinity for muscarinic, cholinergic, histaminergic, or α_1-adrenergic receptors.[16] Several clinical trials have reported the efficacy of this compound in the treatment of patients with moderate-to-severe depression.[17–20] To our knowledge, only a single case report is available regarding the possible benefit of venlafaxine in depression with psychotic features.[21]

The objective of this double-blind, controlled study was to test the effectiveness and tolerability of venlafaxine versus fluvoxamine in delusional depression.

METHOD

Sample

The study group consisted of 30 inpatients consecutively admitted to our Research Center for Mood Disorders for a major depressive episode with psychotic features according to DSM-IV criteria: presence of a major depressive episode (due to a major depressive disorder or to a bipolar disorder and not due to a medical condition or induced by a substance) that is accompanied by mood-congruent or mood-incongruent delusions or hallucinations. Patients with additional diagnoses of Axis I disorders, mental retardation, or severe organic illnesses or who had been taking nonreversible monoamine oxidase inhibitors or slow-release neuroleptics for the last month before admission were excluded. One patient was excluded because the clinical interview revealed the presence of a prior response to fluvoxamine; another did not consent to enter the study. Twenty-eight inpatients gave their written informed consent after a full discussion of the aim and requirements of the study.

The frequencies of the different types of delusions were as follows: guilty, 57.1%; nihilistic, 17.8%; guilty plus paranoid, 14.3%; paranoid, 7.2%; and somatic, 3.6%. Twenty-nine percent of patients had auditory hallucinations; neither visual nor olfactory hallucinations were recorded.

Study Design

A 7-day, single-blind, placebo washout period preceded the 6-week period of active treatment. Physical examinations, laboratory tests, and electrocardiograms were performed. No abnormalities were found.

The 21-item Hamilton Rating Scale for Depression (HAM-D)[22] and the Dimensions of Delusional Experience Rating Scale (DDERS)[23] were used to evaluate severity of illness. The instruments were administered at baseline and every week thereafter by trained psychiatrists who had good interrater reliability and were experienced in psychometric evaluation and blind to treatment option. Side effects were also recorded with the use of the Dosage Records and Treatment Emergent Symptoms Scale (DOTES).[24] No patient was rated as a responder to placebo (20% decrease in HAM-D scores), and no significant side effect was recorded during this period.

Patients (10 male and 18 female; mean ± SD age = 50.7 ± 10.7 years; 6 with bipolar disorder and 22 with unipolar depression) were randomly assigned to 2 therapy groups: fluvoxamine (N = 14) and venlafaxine (N = 14). Randomization was performed by a computer-generated schedule.

The dosage schedule of drugs was as follows: on days 1–3, fluvoxamine, 100 mg, or venlafaxine, 75 mg, both once daily; on days 4–7, fluvoxamine, 100 mg, or venlafaxine, 75 mg, both twice a day; from day 8, fluvoxamine, 150 mg, or venlafaxine, 150 mg, both twice a day. The only other psychotropic drug allowed was flurazepam, up to 30 mg/night. Clinical response was defined as a reduction of HAM-D score to 8 or below and of DDERS score to 0.

Statistical Analyses

Analysis of covariance (ANCOVA), using baseline measures as the covariate, was performed to examine the differences between drug treatments at week 6 for the HAM-D. An intent-to-treat analysis was carried out for all patients who had a baseline assessment and at least 1 assessment after randomization, with the last observation carried forward, on the HAM-D. Student t tests and Fisher exact tests were used as appropriate. All p values were 2-tailed, and statistical significance was set at the 5% level ($p < .05$). Computerized analyses were performed with a commercially available statistical package.[25]

RESULTS

Baseline clinical and demographic characteristics of patients with psychotic depression, grouped according to the treatment, are shown in Table 1. There were no significant differences between groups as determined by Student t tests and Fisher exact tests for continuous variables and frequencies, respectively.

All 14 inpatients who received fluvoxamine completed the study, and 11 (78.6%) of them met the response criteria. Of the 14 patients treated with venlafaxine, 12 (85.7%) completed the study, and 7 (58.3%) of these recovered. Two patients in the venlafaxine group dropped out within 2 weeks of starting treatment because of unpleasant side effects: one patient had increased blood pressure and heart rate, and another reported marked increase of anxiety and agitation. Neither continued in the study.

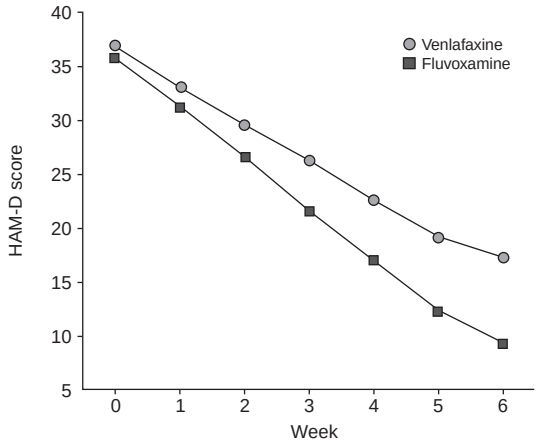
The response rates for fluvoxamine and venlafaxine were compared by the Fisher exact test. No significant difference was found between the drugs when subjects who completed the protocol were considered ($p = .40$).

Table 1. Demographic and Clinical Characteristics of Patients With Delusional Depression[a]

Variable	Treatment Group: Fluvoxamine (N = 14)	Treatment Group: Venlafaxine (N = 14)
Age, y	52.5 ± 9.7	49.0 ± 11.8
Age at onset, y	35.4 ± 12.6	34.4 ± 13.2
No. of previous episodes	4.8 ± 2.5	3.1 ± 2.3
Duration of current episode, wk	10.1 ± 6.1	12.8 ± 5.5
Baseline HAM-D score	35.8 ± 3.8	36.8 ± 3.2
Baseline DDERS score	18.2 ± 2.1	18.8 ± 1.8
Sex, female/male	9/5	9/5
Unipolar/bipolar	11/3	11/3

[a]Data presented as mean ± SD unless specified otherwise. No significant difference was found comparing the 2 treatment groups (Student t test and Fisher exact test for sex and polarity).
Abbreviations: DDERS = Dimensions of Delusional Experience Rating Sale, HAM-D = Hamilton Rating Scale for Depression.

Figure 1. Weekly Time Course of HAM-D Scores in the 2 Therapy Groups



Among all subjects who entered the double-blind study, there was no significant difference between treatments (p = .24). In fact, in the intent-to-treat group 11 (78.5%) of 14 patients taking fluvoxamine and 7 (50.0%) of 14 patients taking venlafaxine were responders.

Figure 1 shows the time course of response. ANCOVA failed to reveal significant differences between the 2 therapy groups (F = 2.34, df = 1,25; p = .14). Neither the exclusion of patients with bipolar disorder (F = 2.10, df = 1,19; p = .16) nor the use of the age at onset as a covariant affected our results (F = 2.58, df = 1,24; p = .12).

Table 2 shows the clinical and demographic characteristics of responders and nonresponders. None of the variables recorded appeared to have an impact on outcome.

Overall, fluvoxamine and venlafaxine were well tolerated. The most common side effects reported by patients included mild nausea and/or gastroenteric troubles, moderate agitation, and somnolence. These side effects persisted only until the third week of treatment. No medically significant adverse events were recorded, except for a marked increase in blood pressure and heart rate observed in one patient who dropped out of the study for this reason.

Table 2. Demographic and Clinical Characteristics of Responders and Nonresponders[a]

Variable	Responders (N = 18)	Nonresponders (N = 8)
Age, y	49.3 ± 10.1	53.7 ± 13.1
Age at onset, y	32.9 ± 11.8	39.6 ± 13.9
No. of previous episodes	3.9 ± 2.5	4.7 ± 2.0
Duration of current episode, wk	13.1 ± 6.5	8.5 ± 2.8
Baseline HAM-D score	35.6 ± 3.8	37.0 ± 2.6
Baseline DDERS score	18.2 ± 2.2	18.9 ± 1.2
Sex, female/male	13/5	6/2
Unipolar/bipolar	15/3	5/3

[a]Data are expressed as mean ± SD unless specified otherwise. No significant difference was found comparing the 2 treatment groups (Student t test and Fisher exact test for sex and polarity).

DISCUSSION

Clinical trials of venlafaxine have demonstrated its efficacy and safety in the treatment of patients with moderate-to-severe depression and refractory depression.[10–13] In addition, it has been proposed that venlafaxine may have a rapid onset of action.[26,27]

To the best of our knowledge, this is the first controlled study of venlafaxine in the treatment of patients with delusional depression. As a matter of caution, given the lack of evidence regarding the use of venlafaxine and the severity of clinical features in delusional depression, we carried out a pilot study. Our results are consistent with those of previously reported studies showing the effectiveness of fluvoxamine for delusional depression[11,12,15] and suggest that venlafaxine may be effective in the treatment of this disorder. No significant differences were found between protocol completers and patients who entered the study (intent-to-treat). Moreover, the weekly time course of response did not significantly differ between the 2 therapy groups. This latter finding suggests, at least in patients with delusional depression treated with high doses, that venlafaxine did not show a more rapid onset of action than fluvoxamine in clinical use. The 2 therapy groups were homogeneous regarding baseline demographic and clinical characteristics, and none of the recorded variables appears to have had an impact on outcome.

The percentage of response in the venlafaxine group appears to be lower than that in the fluvoxamine group, despite the fact that the difference did not reach statistical significance, probably due to the small sample size. For this reason, these findings, although encouraging, need to be replicated in a larger sample in order to ascertain whether venlafaxine is indeed useful in the treatment of delusional depression.

Considering the rapid titration to high doses, the overall safety profile of both fluvoxamine and venlafaxine was favorable, except for 2 patients who dropped out of the venlafaxine group.

One limitation of our study is the lack of a placebo control group, a choice made in accordance with the guidelines of the ethical committee of our hospital because of previously reported lack of placebo response in delusional depressed patients.[28,29]

In conclusion, the results herein presented provide the first clinical evidence that venlafaxine may be a useful and safe compound in the treatment of delusional depression.

Drug names: desipramine (Norpramin and others), fluvoxamine (Luvox), haloperidol (Haldol and others), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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