Venlafaxine in Dysthymic Disorder

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Background: Dysthymic disorder is a chronic depression that is usually characterized by depression rating scale scores that are lower than those for major depressive disorder. Recent studies suggest that pharmacotherapy is quite effective in the treatment of patients with this condition and, in particular, that the newer antidepressants may be better tolerated than older tricyclic antidepressants. The purpose of this study was to investigate the use of a structurally novel antidepressant, venlafaxine, in the treatment of dysthymic disorder.

Method: Seventeen patients with dysthymic disorder were entered into the study, and 14 completed it. A psychiatric interview was used to establish diagnosis, and behavior was assessed by using the Hamilton Rating Scale for Depression (HAM-D) and the Beck Depression Inventory (BDI). Patients were seen over a 9-week period, and venlafaxine treatment proceeded on an open-label basis, from a starting dose of 18.75 mg b.i.d. to a maximum dose of 225 mg/day.

Results: Two patients discontinued early because of side effects, and 1 patient took a single dose, felt better, and did not complete the trial. Analyses of all 17 patients showed significant improvement in HAM-D and BDI scores at the end of the study. Among the completers, there were two response patterns: one group of 7 patients responded quickly to low-dose (75 mg) venlafaxine, and a second group of 7 required the maximum dose. Three of the 7 high-dose patients showed considerable improvement. Side effects in this study were generally in keeping with what has been reported using venlafaxine in treatment of major depressive disorder. No patients evidenced increased blood pressure.

Conclusion: Our study supports the treatment of dysthymic patients with venlafaxine, which has equal efficacy and greater tolerability than tricyclic antidepressants.

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The purpose of this paper is to discuss the use of venlafaxine in the treatment of dysthymic disorder. Dysthymic disorder is a chronic depressive condition. Generally, depression ratings for patients with dysthymic disorder are lower than for patients with major depressive disorder, and dysthymic disorder is often viewed as a mild depressive state. However, dysthymic disorder is associated with considerable psychosocial disabilities.[1,2] The description of dysthymic disorder in DSM-III[3] included its classification as a neurotic depression, and there was a prevailing notion that this mood disorder might be best treated with psychotherapy rather than pharmacotherapy. However, a review of recent studies clearly shows that patients with dysthymic disorder respond to antidepressant pharmacotherapy.[4]

Previous studies have suggested that the tricyclic antidepressants may be poorly tolerated in patients with major depression of mild severity as compared to patients with major depression of moderate or greater severity.[5] Serotonin selective reuptake inhibitors (SSRIs) have been shown to be better tolerated than tricyclic antidepressants in the treatment of major depression, and therefore, SSRIs may be preferable for the treatment of depressed patients with dysthymic disorder.[6] Venlafaxine is a structurally novel antidepressant that blocks the reuptake of serotonin and norepinephrine. The efficacy and safety of venlafaxine have been demonstrated in patients with major depressive disorder.[7–9] The present study was an initial evaluation of venlafaxine in outpatients with dysthymic disorder.

METHOD

This was a 9-week, seven-visit, open-label treatment study for patients who met DSM-IV[10] criteria for dysthymic disorder during 2 or more years prior to entry. All participating subjects gave written informed consent. Subjects were evaluated and then treated with venlafaxine on an open-label basis for 9 weeks. The initial evaluation consisted of a semistructured diagnostic interview to establish diagnosis, a physical examination, and routine laboratory testing. After the evaluation, patients were followed on a weekly basis for the first 3 weeks, and then every other week through Week 9. Doses of venlafaxine began at 37.5 mg/day (18.75 mg b.i.d.) and were titrated according to patient tolerability by 37.5 mg every 2 to 3

days to a target dose of 225 mg/day. For patients who could not tolerate the initial dose of 37.5 mg/day, the dose could be reduced by half and titration could occur more slowly. A minimal dose of 75 mg/day for continuation in the study was required.

Subjects were required to have an entry score of at least 12 points on the 17-item Hamilton Rating Scale for Depression (HAM-D-17).[11] All subjects were 18 years of age or older. Patients could have had a history of other psychiatric conditions such as major depressive disorder 2 years or more prior to study entry. Alcohol or other substance abuse could not have been present for at least 6 months prior to study entry, but in fact no subjects had alcohol or substance abuse for at least 2 years prior to entry. Exclusion criteria included use of other psychotropic medications within 2 weeks prior to study entry (4 weeks for fluoxetine), use of investigational medications within 30 days prior to study entry, presence of an uncontrolled medical disorder or a history of hypertension, and suicidal ideation judged by the clinician to be incompatible with safe study participation.

Assessments included the HAM-D-17 and the Beck Depression Inventory (BDI).[12] Vital signs were assessed at each visit. No other psychoactive medications were permitted nor was psychotherapy allowed during the study period. Medication compliance was assessed by pill counts. At follow-up visits, patients were evaluated by a study psychiatrist (D.L.D. or H.E.H.). Visits were no longer than 15 minutes and were generally according to the format of medication management.[13] Side effects were assessed by the treating psychiatrist by asking the patient about changes in symptoms, medical problems, and use of concomitant medication.

RESULTS

Seventeen patients were entered into this study. Three patients dropped out early, and the results of these patients were available for only baseline and limited follow-up assessment. One patient who dropped out early took one dose of medication, felt better, and returned only once for follow-up a month after the single dose. She had remained euthymic in that interval. A second patient was discontinued because of treatment-emergent side effects involving nausea, panic attacks, anxiety, and insomnia and an inability to increase the dose beyond 18.75 mg/day. This patient discontinued the study at the second visit. A third patient took one dose and discontinued the study because of insomnia. The remaining 14 patients were followed for 9 weeks.

The demographics of the patient sample are presented in Table 1. The patients had a mean age of 40 years and were mildly depressed as evidenced by a mean baseline HAM-D-17 of 17.4 and baseline BDI of 19.8. The duration of the current dysthymic condition was 8.2 years, and patients had a mean of 13.9 years of dysthymia. The mean time depressed was 62.6%. Eleven of the patients were men, and 5 of the patients had never married. Six of the 17 patients were diagnosed as having primary and uncomplicated (having a history of no other Axis I disorder) dysthymia. Thirteen patients had never had a major depressive episode. Three of the patients had dysthymic disorder occurring after a period of marijuana abuse, a major depressive episode, or recurrent major depression (one patient each). One patient had dysthymia complicated by isolated and infrequent panic attacks, 1 by a history of anorexia nervosa, 1 by alcoholism and trichotillomania, 1 by recurrent depression, 2 by marijuana abuse, 1 by marijuana and alcohol abuse, and 1 by alcohol abuse alone. Nine of the patients had had previous psychotherapy. Of 11 patients who had had antidepressant pharmacotherapy, 1 patient did not benefit from an adequate trial (dose and duration) of an antidepressant, 3 had improvement, and 2 showed partial improvement. The trials were limited by early side effects in 2 patients and by inadequate duration in 3 patients.

Table 1: Patient Characteristics*

Variable	Result
Sex	
Men (N)	11
Women (N)	6
Age (y), mean ± SD	40.0 ± 9.0
Duration current dysthymia (y), mean ± SD	8.2 ± 8.3
Percentage of time depressed, mean ± SD	62.6 ± 11.6
Prior psychotherapy (N)	15
Prior pharmacotherapy (N)	10
Prior history of major depressive episode (N)	3
Primary uncomplicated dysthymia (N)	7
Baseline HAM-D, mean ± SD	17.4 ± 3.9
Baseline BDI, mean ± SD	19.8 ± 7.7
Final HAM-D, mean ± SD	7.0 ± 6.1[a]
Final BDI, mean ± SD	7.1 ± 6.2[b]
Final dose (mg/d), mean ± SD	162.5 ± 90.8

*Abbreviations: BDI = Beck Depression Inventory, HAM-D = Hamilton Rating Scale for Depression.
[a]t = 8.18, df = 16, p < .001 compared with baseline.
[b]t = 7.59, df = 16, p < .001 compared with baseline.

Of the fourteen patients who completed treatment, all improved over baseline. A group of 7 patients required the maximum dose of 225 mg/day, and 7 patients responded at 75 mg/day and continued at that dose. Of the 7 patients who required only the minimum dose, all met criteria for recovery of major depressive disorder proposed by Frank et al.[14]: a HAM-D-17 score of 7 or less and a BDI score of 8 or less at endpoint. Six patients had a HAM-D-17 of 4 or less at endpoint and met remission criteria proposed for dysthymic disorder by Thase et al.[15] Of the patients who required 225 mg/day, 3 had a HAM-D-17 of 7 or less and a BDI of 8 or less (2 of these patients had a final HAM-D-17 score of 4 or less), and the other 4 modestly improved over their baseline condition. The mean dose of venlafaxine was 162.5 mg/day, but there was a bimodal distribu-

tion in dosing as noted above. Patients in the low-dose responding group for the most part showed considerable improvement for both the HAM-D-17 and the BDI by the second week of treatment. Ratings for the BDI paralleled changes for the HAM-D-17, and significant ($p < .05$) improvement over baseline ratings was noted by the end of the first treatment week and at each subsequent treatment interval.

Side effects were noted by 13 of the 14 completing patients. For the most part, side effects in these patients were mild and consisted of nausea (10 patients), insomnia (4 patients), headaches (5 patients), sedation (5 patients), dry mouth (4 patients), decrease in appetite (4 patients), constipation (3 patients), sexual dysfunction (3 patients), and light-headedness (3 patients). At the end of the study, medication was tapered over a 1-week period and patients were followed up. No patient had significant discontinuation side effects.

DISCUSSION

In this study, there appeared to be two groups of responders. One group responded quickly to low-dose venlafaxine, and another group required higher doses but ultimately responded, although only half of the latter group recovered. Venlafaxine was well tolerated. Only 2 of the patients discontinued because of side effects, and none of the patients developed increased blood pressure.

It should be pointed out that recovery criteria for dysthymic disorder have not been established but that the recovery criteria proposed by Frank et al.[14] for major depressive disorder and for dysthymic disorder by Thase et al.[15] may provide useful guidelines for improvement of depressive mood disorders. However, dysthymic disorder is a condition characterized by fluctuations and inconsistent symptoms when assessed on a weekly basis, and placebo-controlled trials are clearly necessary to establish efficacy. Although this was not a placebo-controlled study, our results suggest that a significant proportion of dysthymic patients may respond promptly to treatment with low doses of venlafaxine. Another subgroup may require longer treatment at higher doses to achieve response. Perhaps one benefit of the present study is to define a dosing methodology that might be appropriate for a placebo-controlled double-blind study of venlafaxine to more clearly demonstrate its efficacy in dysthymic disorder.

In other studies of patients with dysthymic disorder treated at our site, we have noted improvement with fluoxetine and with cognitive therapy.[16] Other investigators have shown that SSRIs are quite effective in the treatment of dysthymic disorder. Hellerstein et al.[17] reported a significantly greater response rate in dysthymic patients treated with fluoxetine compared with placebo. Open-label studies of fluoxetine have also shown positive results.[18–21] Thase et al.[15] recently reported the results of a large placebo-controlled multicenter trial of sertraline in dysthymic patients who had no history of major depressive episodes. They found sertraline to be superior to placebo in efficacy and to imipramine in tolerability.

Treatment studies of dysthymic patients, with the exception of the study by Thase et al.,[15] involve relatively small sample sizes. Our sample has somewhat different demographic characteristics compared with other treatment samples. Most were men, most were currently married, and most had primary dysthymia that was uncomplicated by comorbid psychiatric conditions. However, the severity of depression ratings is similar to that in other samples. These factors may influence the generalizability of our findings.

In summary, dysthymic disorder is a form of chronic depression. Treatment outcome studies have shown that psychotherapy and pharmacotherapy are effective in alleviating the symptoms of this disorder. Our study supports the treatment of dysthymic patients with venlafaxine. Pharmacotherapy studies increasingly support the use of newer medications, which have equal efficacy but greater tolerability than tricyclic antidepressants, in the treatment of patients with dysthymic disorder.

Drug names: fluoxetine (Prozac), imipramine (Tofranil and others), sertraline (Zoloft), venlafaxine (Effexor).

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