Venlafaxine in the Treatment of Dysthymia: An Open-Label Study

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Background: Numerous studies have demonstrated the effectiveness of antidepressant medications in the treatment of dysthymia, or chronic mild depression. Venlafaxine blocks reuptake of both serotonin and norepinephrine and may produce a more complete antidepressant response than do single-mechanism selective serotonin reuptake inhibitors. The purpose of this open-label study was to provide preliminary data on the tolerability and effectiveness of venlafaxine for patients with dysthymia.

Method: Twenty-two dysthymic subjects (DSM-III-R criteria) were enrolled in this 10-week, open-label trial, and 5 dropped out prior to their second visit. Seventeen subjects (77.3%) received more than 1 week of medication.

Results: Of these 17 subjects, 13 (76.5%) were treatment responders. Results of paired sample t tests were highly significant, indicating that, on average, there was significant improvement on all measures of symptomatology and functioning, with mean ± SD scores on the Hamilton Rating Scale for Depression decreasing from 20.95 ± 6.50 at baseline to 6.06 ± 5.49 at week 10. The mean ± SD final dose was 178.68 ± 70.80 mg/day. Side effects were reported by 17 (85%) of the 20 subjects for whom tolerability was assessed (the most common were fatigue, dry mouth, and nausea); 5 (22.7%) of 22 patients discontinued treatment because of side effects, primarily nausea (N = 3).

Conclusion: These findings suggest the benefit of venlafaxine in the treatment of chronic depression and the need for more rigorous studies.

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In the past several years, numerous studies (see the 1996 review by Dunner[1]) have demonstrated the effectiveness of antidepressant medications in the treatment of chronic depression, a common and debilitating disorder.[2] Medications, including tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs), and selective serotonin reuptake inhibitors (SSRIs), have been shown to alleviate symptoms in patients with a variety of forms of chronic depression,[3–5] including "double depression" (concurrent major depression and dysthymia),[5,6] chronic major depression,[7] and "pure" dysthymia (chronic mild depression).[5,8–11] Depressive symptoms as well as psychosocial functioning have been demonstrated to respond to medication treatment.[5,11,12] The effect of medication is particularly notable since the duration of symptoms prior to treatment is often as much as 30 years.[11]

Venlafaxine is a member of a new generation of selective antidepressants, blocking reuptake of both serotonin and norepinephrine.[13] Theoretically, these dual mechanisms may contribute to a more complete antidepressant response than single-mechanism SSRI medications such as fluoxetine or paroxetine.[14,15] For example, studies have demonstrated the enhanced effectiveness of venlafaxine in treatment-resistant depression.[16] In addition, many SSRI-treated patients may have residual (or recurrent) symptoms,[8,17] and concurrent treatment with medications with different mechanisms of action (such as an SSRI and bupropion) has been recommended for such patients.[18,19] A dual-mechanism medication thus might be of significant benefit. However, it is not clear whether patients with chronic (but relatively mild) symptoms of dysthymia can tolerate the side effects commonly seen with venlafaxine, including nausea, dizziness, somnolence, and sexual dysfunction.[13,20] In 2 recent open-label studies,[21,22] venlafaxine was shown to be well tolerated (with 82.3% of patients in each study completing the protocol) and was effective in alleviating dysthymic symptoms. The purpose of the current study, which had a similar open-label design, was to provide further data on the tolerability and effectiveness of venlafaxine in patients with dysthymia.

METHOD

Patients were recruited through advertisements and public service announcements in the local media. Inclu-

sion criteria included age of 18 to 65 years, a DSM-III-R[23] diagnosis of dysthymia, and a score of 14 or greater on the 24-item Hamilton Rating Scale for Depression (HAM-D).[24] (DSM-III-R diagnosis of dysthymia rather than DSM-IV diagnosis of dysthymic disorder was used because the Structured Clinical Interview for DSM-IV was not available at the time of study initiation.) Exclusion criteria included current major depression (or diagnosis of major depression within the past 6 months); use of other psychotropic medication within the past 2 weeks (4 weeks for fluoxetine); a diagnosis of organic mental disorder, schizophrenia, or bipolar disorder; current pregnancy or nursing (women); drug or alcohol abuse or dependence within the past 6 months; severe medical illness, including uncontrolled hypertension; or current suicidal risk, which could interfere with safe participation with the study. After initial screening for suitability for the study, patients were clinically evaluated by a psychiatrist who obtained psychiatric and medical history, and they underwent laboratory testing including complete blood cell count, blood chemistry screen, urine drug screen, urinalysis, and thyroid function tests.

After admission to the study, patients met every 2 weeks with a psychiatrist for a total of 10 weeks. Patients were started with venlafaxine, 18.75 mg b.i.d., for 4 days, then increased to 37.5 mg b.i.d. (to minimize nausea at the initiation of treatment). At 2 weeks, dosage was increased to 75 mg b.i.d. if clinically tolerated, and then increased by 75-mg increments if clinically indicated. Maximum dose was 350 mg/day. At each visit, physicians assessed patients' vital signs and administered rating scales, including the 24-item HAM-D,[24] the Cornell Dysthymia Rating Scale (CDRS),[25] the Clinical Global Impressions scale (CGI)[26] (including patient and clinician ratings), and the Global Assessment of Functioning (GAF),[27] as well as clinically oriented safety and side effect evaluations. Patients completed 2 self-report inventories at each visit: the Beck Depression Inventory (BDI)[28] and the Symptom Checklist-90-Revised (SCL-90R).[29]

Twenty-two subjects who met DSM-III-R[23] criteria for dysthymia using the Structured Clinical Interview for DSM-III-R (SCID) semistructured interview[30] were enrolled into the 10-week open-label study after providing informed consent to study procedures that had been explained to them. Five subjects dropped out prior to their week 2 visit, primarily because of side effects (the most frequently reported side effect that caused subjects to discontinue treatment was nausea); thus, 17 subjects (77.3%) received more than 1 week of medication, and these subjects are described in the Results section of this report.

Statistical Analyses

Efficacy was evaluated using responder analyses and paired t tests. Subjects were categorized as responders (or remitters) using 2 separate criteria, and the proportion of treatment response or remission was calculated. Mean time to response was assessed by charting efficacy measures at each 2-week interval. Changes on measures of symptoms and global functioning were analyzed using paired sample t tests, and statistical significance was defined as $p \leq .05$ using 2-tailed tests. Last-observation-carried-forward (LOCF) data were used. Frequency of side effects is reported.

RESULTS

Patient Characteristics

Of the 22 subjects, 15 (68%) were women, and 18 (82%) were white, with a mean ± SD age of 45.7 ± 10.7 years. Sixteen (73%) were diagnosed with early onset dysthymia, and 18 (82%) had previous episodes of major depression (mean ± SD number of episodes = 3.1 ± 4.3). Eleven (50%) subjects had a comorbid Axis II diagnosis. Five (23%) of the subjects had current comorbid Axis I diagnoses, including generalized anxiety disorder (GAD) (N = 4) and eating disorder (N = 1), and 4 (18%) had past diagnoses of drug abuse or dependence. The mean ± SD daily dose at the end of treatment was 178.68 ± 70.80 mg (range, 75–300 mg/day).

Of the 17 subjects who received medication for more than 1 week, responders (N = 13) had a mean ± SD dose of 164.4 ± 54.2 mg/day, with 30.8% (N = 4) responding at doses under 150 mg/day and 69.2% (N = 9) responding at doses equal to or greater than 150 mg/day. Nonresponders (N = 4) had a mean ± SD final daily dose of 225 ± 106.1 mg. Nonresponders had a higher mean ending dose owing to increases in dosage made in response to lack of efficacy. Responders (N = 13) were treated with daily doses as follows: 75 mg (N = 1); 112.5 mg (N = 3); 150 mg (N = 4); 225 mg (N = 5). Nonresponders (N = 4) were treated with the following daily doses: 75 mg (N = 1); 225 mg (N = 1); 300 mg (N = 2).

Study noncompleters did not differ from completers in demographics, onset, Axis I or II comorbidities, number of prior depressive episodes, or baseline rating scale scores. There were differences with age at onset, with more childhood-onset subjects dropping out (80.0%; N = 4 of 5) than adolescent-onset (18.2%; N = 2 of 11) or adulthood-onset subjects (16.7%; N = 1 of 6) ($\chi^2 = 6.93$, df = 2, p = .03).

Tolerability

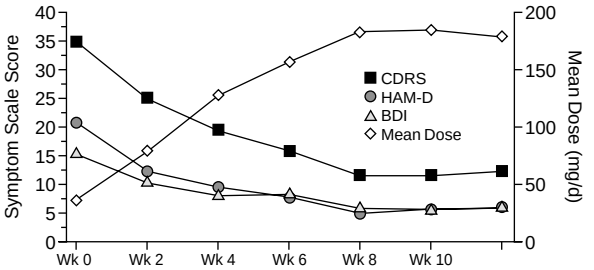
Of the 20 patients for whom information on side effects was collected, 17 (85%) reported at least 1 side effect. The following side effects were reported: fatigue (25%; N = 5), dry mouth (15%; N = 3), nausea (15%; N = 3), dizziness (10%; N = 2), delayed ejaculation/orgasm (10%; N = 2), palpitations or increased heart rate (10%; N = 2), decreased libido (10%; N = 2), anxiety

Table 1. Scores on Dependent Measures at Week 0 and at the End of Treatment[a]

	Week 0 (N = 22)		End of Treatment (N = 17)		
Scale	Mean	SD	Mean	SD	t (df = 16)
BDI	15.27	4.42	6.29	4.61	9.83*
CDRS	35.27	9.21	12.24	10.42	7.58*
HAM-D	20.95	6.50	6.06	5.49	7.75*
GAF	62.55	5.10	75.94	9.99	–4.63*
SCL-90R	1.26	0.48	0.41	0.38	8.33*
CGI-S	3.48	0.86	1.94	1.03	6.15*

[a]Ratings from week 10 or the last observation carried forward (LOCF). Abbreviations: BDI = Beck Depression Inventory, CDRS = Cornell Dysthymia Rating Scale, CGI-S = Clinical Global Impressions-Severity of Illness scale, GAF = Global Assessment of Functioning, HAM-D = Hamilton Rating Scale for Depression, SCL-90R = Symptom Checklist-90-Revised.
*p < .001.

Figure 1. Measures of Depression Symptomatology and Medication Dosage: Biweekly Mean Score



Scale	Wk 0 (N = 22)	Wk 2 (N = 17)	Wk 4 (N = 17)	Wk 6 (N = 15)	Wk 8 (N = 14)	Wk 10 (N = 14)	LOCF
CDRS	35.27	24.94	19.44	15.93	11.71	11.71	12.24
HAM-D	20.97	12.29	9.65	8.00	5.07	5.71	6.06
BDI	15.27	10.41	8.06	8.33	5.92	5.79	6.29
Mean Dose	37.50	79.41	127.94	157.03	183.48	184.62	178.68

(10%; N = 2), and sweating or night sweats (10%; N = 2). The following side effects were reported by 5% of patients (1 patient each): insomnia, decreased appetite, erectile dysfunction, gastrointestinal upset, loose stools, constipation, hand tremor, restlessness, headaches, and increased blood pressure. Five patients (22.7% of the intent-to-treat [ITT] sample) discontinued treatment owing to side effects: nausea (N = 3), which co-occurred with dizziness in 2 of these patients; increased blood pressure (N = 1); and feelings of unreality (N = 1). Three patients ended treatment for other reasons (including 1 who decided she did not want to receive medicine, and 2 for unknown reasons).

Efficacy Analyses

Treatment response. Subjects were categorized as responders if they showed a 50% or greater decrease in HAM-D scores from week 0 and a CGI-Improvement score of 1 ("very much improved") or 2 ("much improved"). Thirteen subjects (76.5% of the treatment-exposed sample, 59.1% of the ITT sample) were classified as treatment responders. Paired sample t tests were conducted and are reported in Table 1, which also reports mean ± SD scores at week 0 for the entire sample of 22. All t tests were highly significant, indicating that, on average, there was significant improvement on all measures of symptomatology and functioning.

Figure 1 depicts the mean score on the 3 measures of depressive symptomatology at 2-week intervals, the mean LOCF scores for those who received an adequate course of treatment, and the mean dose of venlafaxine at each interval. The mean scores on the HAM-D fell below the standard responder cutoff of 8 at week 8, on the BDI (cutoff = 10) at week 4, the CDRS (cutoff = 20) at week 4, and the CGI-Severity of Illness scale (cutoff = 2) at week 8. The SCL-90R does not have a standard responder cutoff, and thus this scale was not included in these analyses. For those who were classified as responders according to the first set of criteria (N = 13), 1 (7.7%) subject met criteria for response at week 2, 4 (30.8%) at week 4, 6 (46.2%) at week 6, and 2 (15.4%) at week 8 (mean ± SD time to response was 5.38 ± 1.70 weeks). The mean ± SD dose at the time of response was 141.35 ± 40.95 mg/day.

Remission. We also categorized patients as remitters using criteria developed by Thase et al.,[10] including (1) absence of a DSM-III-R diagnosis of dysthymia at the end of treatment and (2) a score on item 1 of the HAM-D (depressed mood) of 0 ("absent"). Since we did not conduct SCID interviews at the end of treatment, we have used the CDRS and HAM-D items as rated by the treating clinicians as evidence of the presence or absence of symptoms from which to infer the final diagnosis. Using these criteria, 12 patients (70.6% of completers, 54.5% of the ITT sample) were remitters.

DISCUSSION

Tolerability

The dropout rate in studies of dysthymia has varied with different medications. In a recent study,[10] 84% of sertraline-treated subjects completed a 12-week study, in comparison with 67% receiving imipramine and 76% receiving placebo; the dropout rates due to adverse events were 6% for sertraline, 18% for imipramine, and 5% for placebo. In the study of venlafaxine recently reported by Dunner et al.,[21] 82.4% (14/17) of patients completed a 9-week protocol, and in the study by Ravindran et al.,[22] 82.4% (14/17) completed the 12-week protocol. In the present study, 14 (63.6%) of 22 subjects completed a 10-week protocol. Five patients (22.7%) dropped out owing to adverse events, and 3 for other reasons. Overall, the completion rate in the venlafaxine studies of dysthymia appears to approximate that found for tricyclic antidepressants. The discontinuation rate is also comparable to that for venlafaxine in major depression due to adverse

Table 2. Response to Treatment in Studies of Dysthymic Patients[a]

Study			HAM-D						
Medication	Authors	Duration (wk)	No. of items	Pretreatment Score (mean ± SD)	Posttreatment Score (mean ± SD)	Percent Change Score	Attrition Rate (%)	Response Rate (%)[b]	Remission Rate (%)[c]
Fluoxetine	Hellerstein et al[8]	8	24	19.2 ± 4.3	9.7 ± 4.8	49.6	8.6	62	N/A
Imipramine	Thase et al[10]	8	17	13.4 ± 3.8	N/A	34.7	33.0	64	44
Sertraline	Thase et al[10]	8	17	12.7 ± 4.0	N/A	32.9	16.0	59	50
Venlafaxine	Dunner et al[21]	9	17	17.4 ± 3.9	7.0 ± 6.1	61.2	17.7	71	57
Venlafaxine	Present study	10	24	20.9 ± 6.4	6.1 ± 5.5	61.7	22.7	77	71
Venlafaxine	Ravindran et al[22]	12	17	15.9 ± 4.0[c]	3.8 ± 4.2[d]	76.1	17.6	73	N/A

[a]Abbreviation: N/A = not available.
[b]Response defined as follows: Hellerstein et al.: 50% decrease in HAM-D score and CGI-Improvement (CGI-I) score ≤ 2 ("very much" or "much" improved); Thase et al.: CGI-I rating ≤ 2; Dunner et al.: "recovery" HAM-D score ≤ 7 and BDI score ≤ 8 (see Frank et al.[32]); Ravindran et al.: 50% or greater decrease in HAM-D score.
[c]Remission using criteria of Thase et al.[10]: HAM-D score ≤ 4, HAM-D item 1 = 0, no longer meets DSM criteria for dysthymia.
[d]Means and standard deviations obtained by written communication from A. V. Ravindran, M.D., Ph.D., 1999.

events in Phase 2 and 3 studies,[31] a rate of 19%. Interestingly, in the present study most dropout appeared early in treatment and was associated with an early age at onset of symptoms.

Efficacy

Our results suggest that if side effects do not interfere with the initiation of treatment, most dysthymic patients show a positive response to venlafaxine. In this study, 76.5% of the treatment-exposed cohort showed a significant response to treatment, and 70.6% entered remission (see Results section for definitions). The overall response rate for the ITT sample was 59.1%. Significant improvement was found on a variety of self-report and clinician-report ratings, including symptom severity, overall severity of illness, and psychosocial functioning. These findings are similar to those reported by Dunner et al.[21] and Ravindran et al.[22] In the absence of a placebo control group, findings must be tentative (in other studies at our site with similar methodology, patient selection criteria, and rating instruments, placebo response rates ranged from 18.8%[8] to 44%[10]).

Magnitude of Response

The magnitude of symptom response to venlafaxine can be compared to that found in other studies not only with venlafaxine,[21,22] but also with the SRI medications fluoxetine[8] and sertraline,[10,20] as well as tricyclics such as imipramine[10,20] and the noradrenergic agent desipramine[5] (Table 2). The scores on depression rating scales in this study (baseline 24-item HAM-D score of 20.87 ± 6.36, final score of 6.06 ± 5.49, with a mean change of approximately 14.8 points) suggest a response at least as robust as has been demonstrated with these other medications. For instance, in our center's double-blind study with fluoxetine,[8] 24-item HAM-D scores decreased from 19.20 ± 4.33 to 9.67 ± 4.85 at week 8, an average drop of 9.53 points. In a recent large study[10] comparing sertraline, imipramine, and placebo, sertraline treatment was associated with a 5.6 ± 6.1 point decrease in 17-item HAM-D score from 12.7 at baseline (or 9.2 points on the 29-item HAM-D); imipramine treatment was associated with a change of 5.9 ± 5.8 points in 17-item HAM-D score from 13.4 at baseline and a drop of 10.2 points on the 29-item version. Additionally, in Dunner's venlafaxine study,[21] there was a large decrease (10.4 points) in 17-item HAM-D score. Given the current study's small sample size and lack of placebo or active controls, it is not possible to determine whether there is an additional benefit from venlafaxine's dual mechanism of action. Some[33–35] but not all[36,37] evidence suggests that this dual action occurs primarily at the higher dosage range. Five (38%) of our responders and 3 (75%) of our nonresponders were receiving doses above 200 mg/day. The evidence regarding the dose-dependent dual action effect is largely from animal studies, and human studies of sustained treatment have been done with low (75 mg/day) or high (375 mg/day) doses,[35] with minimal information available for intermediate doses. Thus, further studies seem warranted.

Time to Response

The average time to response in this study was 5.38 weeks, with 75% of the responders showing a good clinical response between weeks 4 and 6. The mean dose at which subjects responded to treatment was 141.35 mg/day.

Limitations of the Study

Clearly, the open-label design and the lack of placebo control limit the generalizability of our study data. However, our study used experienced investigators and raters in a center with extensive prior experience in conducting studies of dysthymia.

CONCLUSION

Open-label data from our study and others[21,22] support the hypothesis that venlafaxine is an efficacious and rela-

tively well-tolerated treatment for the symptoms of chronic depression. The initial high rate of dropout occurred despite a slow initiation of treatment (18.75 mg b.i.d.); it is possible that starting treatment even more slowly (e.g., 18.75 mg/day for several days, then b.i.d.) might lead to less dropout. The extended-release form of venlafaxine (venlafaxine XR) might also show a higher degree of tolerability, given its more prolonged pharmacokinetic profile,[38] with less peak-to-trough fluctuation and a more gradual slope to its kinetic curve, and findings[39] that it has higher tolerability and efficacy than the immediate-release form. For those dysthymic patients who tolerate an adequate trial of medication, there appears to be a robust response to venlafaxine, perhaps greater than seen with SSRIs or tricyclics, suggesting a role for venlafaxine in dysthymics with partial response to other medications or with residual symptoms that impair functioning. Clearly, there is a need for double-blind prospective studies comparing venlafaxine both with placebo and with other medications, assessing initial and sustained response to treatment.

Drug names: bupropion (Wellbutrin), desipramine (Norpramin and others), fluoxetine (Prozac), paroxetine (Paxil), sertraline (Zoloft), venlafaxine (Effexor).

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