A Large Open-Label Study of Venlafaxine in Depressed Outpatients by Community-Based Physicians

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Background: Studies to date suggest that venlafaxine is effective, well tolerated, and safe in a broad spectrum of patients. We examined the clinical utility and tolerability of venlafaxine in patients treated by community-based psychiatrists and family physicians in a naturalistic clinical setting.

Method: Nineteen physicians each recruited 10 to 20 physicians to enroll 5 patients each maximum, diagnosed with DSM-IV major depression or dysthymia. The patients were at least moderately ill (Clinical Global Impressions) with a score of at least 32 on the Zung Self-Rating Depression Scale. After baseline clinical and laboratory assessments, each patient received 37.5 mg of venlafaxine b.i.d., with adjustments possible at the 5 visits during the next 8 weeks.

Results: Of the 880 patients at baseline, 682 completed the 8-week study. The daily doses of venlafaxine ranged between 18.75 mg and 375 mg, with 80% receiving between 75 and 150 mg/day by 8 weeks. The intent-to-treat analysis revealed that at 8 weeks, 62% (522 of 843) of patients were either much or very much improved. Nausea was the most frequent side effect, followed by somnolence, headache, and dry mouth.

Conclusion: Venlafaxine has good clinical utility and tolerability in a community-based sample of a broad spectrum of depressed outpatients.

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Venlafaxine is the first of a new class of antidepressants, the serotonin and norepinephrine reuptake inhibitors (SNRIs). In preclinical studies, it has been shown to produce a dose-dependent inhibition of the neuronal reuptake of serotonin and norepinephrine without any significant affinity for muscarinic, histaminergic, and α_1-adrenergic receptors.[1,2]

Venlafaxine has been shown to have a broad spectrum of efficacy in depressed patients.[3] In randomized controlled trials, it has been shown to be effective in the treatment of outpatients with major depression,[4–12] as well as in the treatment of severely depressed inpatients with melancholia.[13–15] Venlafaxine has also been shown to be an effective treatment for patients with treatment-resistant chronic depression.[16] The majority of patients responded to venlafaxine at doses of 75 to 150 mg/day,[7,11,12] whereas more severely ill patients responded to increased doses within a recommended dose range of 75 to 375 mg/day.[13,14,16]

A meta-analysis of controlled trials suggests that venlafaxine is an effective antidepressant that is well tolerated and has a good safety profile.[3] These observations would suggest that venlafaxine would have broad appeal as a first-line antidepressant for the treatment of patients with major depression in a general clinical practice setting. Data on the use of venlafaxine in a clinical practice setting rather than a research setting are limited.[17,18] We therefore carried out an open-label study of the clinical utility and tolerability of venlafaxine in a large cohort of patients treated by community-based psychiatrists and family physicians in a naturalistic clinical setting.

METHOD

The multicenter study was conducted across Canada using a hub-and-spokes administrative arrangement. Each of 19 physicians (hubs) in major cities across the country was responsible for recruiting 10 to 20 investigators (spokes) in his or her respective geographical region. The patients' data forms were transported to the hubs where computerized remote data entry procedures were followed to transmit the data to a contracted data-processing research organization. The protocol and consent form were approved by a central independent ethics review board, and all patients gave oral and written consent to participate in the study.

Depressed outpatients were entered into the study by 211 community-based physicians (149 family physicians and 62 psychiatrists) located across Canada. Each physician was allowed to enter a maximum of 5 patients in the study. All physicians received a thorough orientation in the diagnosis of depression, principles of management of

depression, and the proper use of venlafaxine to ensure the same standard of knowledge at the beginning of the study. All patients were entered into the study between July and November 1995. All physicians also received an additional supervisory session during the period of recruitment.

Male and female outpatients between the ages of 18 and 70 years were enrolled. All patients had received the diagnosis of major depression or dysthymia by their physician. Specifically, the physicians were informed about the DSM-IV criteria for major depressive disorder and were instructed to apply a clinical diagnosis so as to replicate best the usual clinical condition. The clinical diagnosis was consistent with DSM-IV criteria and required patients to demonstrate a currently depressed mood (depressed, sad, hopeless, discouraged, down in the dumps) and/or loss of interest or pleasure in all or almost all usual activities and pastimes. In the clinical assessment, patients had to have a baseline rating of at least 4 (moderately ill) on the 7-point Severity of Illness scale of the Clinical Global Impressions (CGI) assessment,[19] as determined by the physician, and a raw score of at least 32 (percent index = 40; 32 out of a maximum score of 80) on the Zung Self-Rating Depression Scale (SDS).[20]

Patients were excluded from the study if they had had a previous trial of venlafaxine for their current major depressive episode. Pretrial use of certain other antidepressants was prohibited. Specifically, no monoamine oxidase inhibitors were permitted within 14 days of starting venlafaxine. Known hypersensitivity to venlafaxine, use of fluoxetine within 21 days of starting venlafaxine, and use of any investigational drug within 30 days of starting venlafaxine excluded patients from the trial. Patients known to have displayed drug-seeking behavior for prescription centrally acting drugs during the past 12 months were also excluded. During the study, use of antidepressants other than venlafaxine was prohibited, as was the use of any investigational drugs. Females of childbearing potential had to have a negative β-human chorionic gonadotropin test response immediately prior to starting venlafaxine therapy and had to use an effective, medically acceptable contraceptive throughout the study. Lactating females were excluded from the study.

At baseline, a complete psychiatric and medical history was taken, including a diagnostic interview to confirm the diagnosis of depressive disorder. This included the following information: age, sex, current and past illness, current and prior treatments, history and course of prior psychiatric illness, description of prior treatments, and description of the current episode. A physical examination was conducted, including vital signs and weight measurements, as well as a routine laboratory screening (hematology, blood chemistry, and qualitative urinalysis) and a measurement of thyroid-stimulating hormone. Venlafaxine (Effexor, Wyeth-Ayerst Canada Inc., St-Laurent, Quebec) was initiated and treatment proceeded in the usual clinical manner.

At baseline, the patients were to receive venlafaxine 37.5 mg b.i.d. orally for about 2 weeks, and thereafter the dose could be adjusted within the range of 37.5 to 375 mg/day, with the aim of optimizing the response. Physicians were permitted to adjust the venlafaxine dose according to their clinical judgment. The medication was provided in the open-label form at each visit, with changes in dosage recorded at the respective visits. If venlafaxine was discontinued, a 6-day tapering period was recommended, approximately halving the dosage every 3 days.

Patients were classified as suffering from acute or chronic depression depending on whether the episode had lasted less than or at least 2 years, respectively, according to the DSM-IV definition for the chronicity of depression. At 1, 2, 4, 6, and 8 weeks, patients were evaluated for the severity of and any change in their depression. The assessments during the treatment period included the Severity of Illness and Global Improvement sections of the CGI and the SDS.

Study events as well as use of concomitant medications were recorded at each visit. At the time of the final visit, laboratory investigations were repeated, as were blood pressure measurements, heart rate, and weight. If a patient discontinued venlafaxine, a poststudy visit was held between 4 and 10 days after discontinuation to review any and all signs and symptoms and the use of any concomitant medications or therapy.

Statistical Analysis

The primary response variable was the proportion of patients who had a clinically good outcome, defined as a CGI Global Improvement score of 1 or 2. The last-observation-carried-forward (LOCF) method, in which the last CGI Global Improvement score for a withdrawn patient was carried forward into all subsequent time periods, was used for withdrawn patients.

The intent-to-treat analysis was the primary analysis, which included all enrolled patients who had at least 1 baseline evaluation on 1 of the primary efficacy variables, received at least 1 dose of drug, and had at least 1 efficacy evaluation while on treatment. The primary response variable also was analyzed using 2 additional methods: an observed-case analysis and a per-protocol analysis. The observed-case analysis was based on all available data at the respective time points (baseline, 1, 2, 4, 6, and 8 weeks). The per-protocol analysis was based on patients who completed the 8-week period of study. The secondary response variable was the index score of the SDS. Patients who had answered at least 18 of the 20 items on the SDS were included in the analyses.

The chi-square test was used in comparing proportions, and the t test was used in comparing 2 means. Repeated measures analysis of variance (ANOVA) was used

Table 1. Baseline Demographic and Clinical Characteristics of the Study Population (N = 880)

Variable	Result
Sex	
Female	582
Male	298
Age (y)	
Mean ± SD	41.9 ± 11.3
Range	18–70
Weight (kg)[a]	
Mean ± SD	74.7 ± 18.3
Range	41–163
Duration (wk) of depressive episode	
Mean ± SD	3.6 ± 7.2
Range	0–55
Type of depressive episode	
Major depression	850 (97%)
Dysthmia	30 (3%)
Recurrent depression	306 (35%)
Time frame of current illness	
Acute	622 (71%)
Chronic	258 (29%)
CGI Severity of Illness	
4: Moderately ill	496 (56%)
5: Markedly ill	313 (36%)
6: Severely ill	70 (8%)
7: Extremely ill	1 (0%)
Zung Self-Rating Depression Scale[b]	
Mean ± SD	71.2 ± 10.2
Range	40–96

[a]N = 879.
[b]N = 876.

Table 2. Reasons for Premature Discontinuation From the Study

Reason for Discontinuation	Number (%) of Patients
Total	198 (22.5)
Adverse reaction	134 (15.2)
Failed to return	18 (2.0)
Unsatisfactory response	17 (1.9)
Patient request	12 (1.4)
Protocol deviation	9 (1.0)
Other medical/nonmedical event	8 (0.9)

on the CGI Global Improvement scores and the SDS for assessment of the time effect.

RESULTS

Nine hundred eleven patients were enrolled in this study. Thirty-one patients were excluded for protocol violation, leaving 880 patients eligible for analysis. Demographic and clinical characteristics at baseline are displayed in Table 1. The majority (97%) of patients had major depression characterized as an acute illness (71%), and most patients were either moderately or markedly ill according to the baseline CGI score.

Of the 880 patients at baseline, 682 completed the required 8 weeks of treatment. The intent-to-treat analysis included 843 patients who had CGI data available at week 1, and the observed-case and per-protocol analyses included 701 patients with CGI data available at week 8. Ninety-nine patients withdrew during the first 2 weeks of treatment, with the same number withdrawing during the remaining 6 weeks. Overall, 22.5% of patients withdrew from the study prematurely, and adverse reaction in 134 patients (15%) was the most common reason for early discontinuation from the study (Table 2). Only 17 patients withdrew from the study due to lack of response to the antidepressant medication. All 17 of these patients had taken venlafaxine for at least 2 weeks. After therapy was initiated, the daily dosages of venlafaxine ranged from 18.75 mg to 375 mg/day. After 8 weeks of therapy, 537 (80%) of the 674 patients with confirmed dose levels were receiving between 75 and 150 mg/day.

The CGI Global Improvement scores for the intent-to-treat, observed-case, and per-protocol analyses are shown in Table 3. For the intent-to-treat analysis, a clinically good outcome (CGI score of 1 = very much improved or 2 = much improved) was observed in 522 (62%) of the 843 patients analyzed at 8 weeks of treatment. For both the observed-case and the per-protocol analyses, 72% (503 of 701 patients) had a clinically good outcome. When the proportion of patients with a clinically good outcome was analyzed according to dose level, the optimal response occurred with a daily dosage greater than 37.5 mg and less than or equal to 75 mg (Figure 1). Of the 319 patients who had taken no antidepressant medication during the year prior to the study, 69% experienced a clinically good outcome, whereas 58% of those who had taken at least 1 antidepressant medication during the year experienced a clinically good outcome ($p < .002$, chi-square test).

The SDS percent index scores for the intent-to-treat, observed-case, and per-protocol analyses are shown in Table 3. Among 316 patients who received venlafaxine as first-line therapy, the mean SDS percent index at week 8 was 50.0 ± 15.0 compared with 56.5 ± 15.8 among 514 patients who received other antidepressants prior to venlafaxine ($p < .001$, t test). When the distribution of SDS scores was analyzed according to dose level, the optimal response occurred with a daily dosage greater than 37.5 mg and less than or equal to 75 mg (Figure 1).

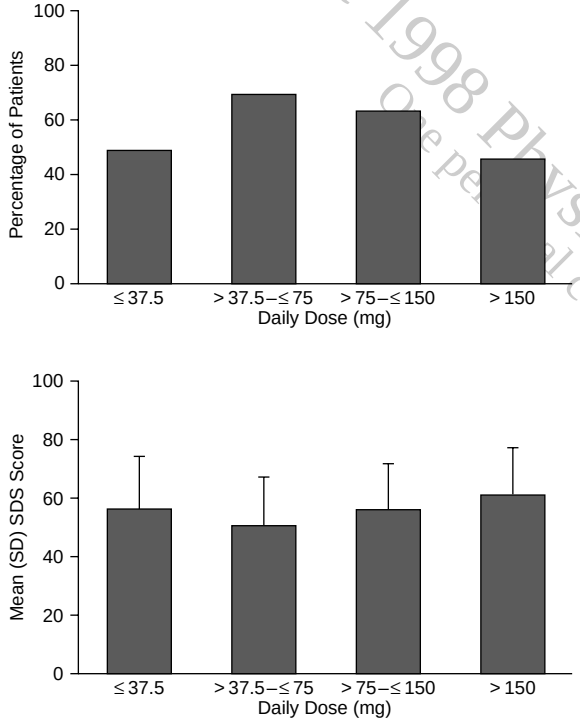
Repeated measures ANOVA for the CGI Global Improvement scores of 691 analyzable patients showed a significant change in score over time ($F = 318.56$, $df = 4,2760$; $p < .0001$). Similarly, repeated measures ANOVA for the SDS percent index indicated a significant change ($F = 527.48$, $df = 5,3370$; $p < .0001$). When the CGI improvement scores and the SDS indices were examined using the observed-case analysis method or the per-protocol analysis method, the results were similar to the ANOVA findings.

The most commonly reported adverse events with venlafaxine are displayed in Table 4. Nausea was the most common adverse event reported in 39% of patients; how-

Table 3. CGI Global Improvement and SDS Scores From Intent-to-Treat, Observed-Case, and Per-Protocol Analyses

	Intent-to-Treat			Observed Case			Per Protocol		
Visit	Patients (N)	Mean	SD	Patients (N)	Mean	SD	Patients (N)	Mean	SD
CGI Global Improvement scores									
1 Week	843	3.43	0.85	843	3.43	0.85	705	3.36	0.82
2 Weeks	843	3.04	0.96	795	2.98	0.92	706	2.93	0.90
4 Weeks	843	2.84	1.14	768	2.74	1.10	706	2.66	1.04
6 Weeks	843	2.60	1.21	721	2.42	1.11	698	2.36	1.05
8 Weeks	843	2.36	1.25	701	2.07	1.03	701	2.07	1.03
SDS scores									
1 Week	830	64.6	12.2	830	64.6	12.2	691	64.4	12.1
2 Weeks	830	60.8	13.1	789	60.8	13.2	693	60.5	13.0
4 Weeks	830	58.7	14.7	760	58.4	14.8	692	58.1	14.5
6 Weeks	830	56.1	15.6	712	55.1	15.4	686	54.8	15.2
8 Weeks	830	54.0	15.8	696	52.4	15.4	696	52.4	15.4

Figure 1. Distribution of Patients With a Clinically Good Outcome (top panel) and SDS Indices (bottom panel) According to Dose Level (Intent-to-Treat Analysis)



ever, the incidence of nausea was highest during the first week of therapy (32%), declined rapidly to 11% by week 2, and remained at this low level to the end of treatment. Similarly, the incidence of headache was highest (15%) during week 1, but decreased to 6% by week 8.

Among 501 patients with a baseline diastolic blood pressure less than 90 mm Hg, a mean ± SD increase of 0.6 ± 9.2 mm Hg was observed at study end. Among 67 patients with a diastolic pressure ≥ 90 mm Hg at baseline, a mean decrease of 6.8 ± 9.2 mm Hg was observed at study end. No differences in age, sex, or weight were noted between patients with or without recorded blood pressure measurements. There were no clinically important changes in pulse, weight, or any laboratory test results.

Table 4. Summary of Most Common Treatment-Emergent Adverse Events

Event	Number (%) of Patients
Nausea	346 (39)
Headache	219 (25)
Insomnia	181 (21)
Dry mouth	136 (15)
Constipation	127 (14)
Dizziness	121 (14)
Somnolence	117 (13)
Sweating	108 (12)
Asthenia	85 (10)

DISCUSSION

We observed that, in a large cohort of depressed outpatients treated by community-based physicians, venlafaxine is an effective and well-tolerated antidepressant treatment, as evaluated systematically for clinical response and safety. Our data suggest that the majority of depressed patients responded to venlafaxine and that 75 mg/day was the optimal dose. The results of the CGI and SDS assessments show that venlafaxine was effective in ameliorating depression, as determined by either a physician rating scale or a patient rating scale. Furthermore, no matter which of the 3 methods of statistical analysis was used to examine the data (intent-to-treat, observed-case, per-protocol), the findings were similar for the CGI improvement scores and for the SDS indices.

Patients who had taken no antidepressant medication during the year prior to the study were more likely to experience a clinically good outcome than were those who had taken medication. In both cases, however, a patient was more likely to experience a good clinical outcome than not. This finding suggests that if patients take venlafaxine tablets as their first antidepressant medication, a positive response is probable. It also suggests that even if

patients have taken other antidepressant medication during the previous year, patients show an improvement with venlafaxine.

Overall, venlafaxine was well tolerated. Nausea was the most common adverse event reported, but consistent with other reports,[21] its occurrence was transient as evidenced by a rapid decrease in the incidence within 2 weeks after initiation of therapy. Data on blood pressure were available from only 57% of patients because blood pressure assessment was not required when the study was initiated. A review of baseline demographic and clinical characteristics revealed no differences between patient groups with and without blood pressure assessments at baseline. Review of the data collected on blood pressure shows that no clinically significant changes occurred during treatment. Patients with the higher diastolic pressure readings actually experienced a decrease in diastolic pressure by study end. The lack of effect on vital signs and laboratory tests reflects what has been observed in other clinical studies with venlafaxine.[13,14,18]

This was an open-label study using a self-rated scale and a physician-rated scale for assessing patients with moderate-to-severe depression that would be consistent with a typical diagnostic assessment performed in a general practice setting. The purpose of this study was not to document the efficacy of venlafaxine, which has been well established.[3–12] Rather, it was to determine whether venlafaxine if used in a naturalistic setting would provide effective, well-tolerated antidepressant therapy. These results are consistent with other open-label trials where response rates of 60% to 70% and discontinuation rates of 15% to 25% have been reported during short-term treatment.[22–25] This trial builds on the findings with venlafaxine reported for a study in a smaller population,[17] by including assessment of the severity and chronicity of depression and by appraising the responses to different dose levels. Our data show that venlafaxine has good clinical utility and tolerability in a community-based sample of a broad spectrum of depressed outpatients. The majority of patients responded to venlafaxine 75 mg/day.

Drug names: fluoxetine (Prozac), venlafaxine (Effexor).

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REFERENCES

1. Muth EA, Haskins JT, Moyer JA, et al. Antidepressant biochemical profile of the novel bicyclic compound Wy-45,030, an ethyl cyclohexanol derivative. Biochem Pharmacol 1986;35:4493–4497
2. Muth EA, Moyer JA, Haskins JT, et al. Biochemical, neurophysiological, and behavioral effects of Wy-45,233 and other identified metabolites of the antidepressant venlafaxine. Drug Dev Res 1991;23:191–199
3. Entsuah AR, Rudolph RL, Chitra R, et al. Effectiveness of venlafaxine treatment in a broad spectrum of depressed patients: a meta-analysis. Psychopharmacol Bull 1995;31:759–766
4. Khan A, Fabre LF, Rudolph R, et al. Venlafaxine in depressed outpatients. Psychopharmacol Bull 1991;27:141–144
5. Schweizer E, Feighner J, Mandos LA, et al. Comparison of venlafaxine and imipramine in the acute treatment of major depression in outpatients. J Clin Psychiatry 1994;55:104–108
6. Shrivastava RK, Cohn C, Crowder J, et al. Long-term safety and clinical acceptability of venlafaxine and imipramine in outpatients with major depression. J Clin Psychopharmacol 1994;14:322–329
7. Dierick M, Ravizza L, Realini R, et al. A double-blind comparison of venlafaxine and fluoxetine for treatment of major depression in outpatients. Prog Neuropsychopharmacol Biol Psychiatry 1996;20:57–71
8. Cunningham LA, Borison RL, Carman JS, et al. A comparison of venlafaxine, trazodone, and placebo in major depression. J Clin Psychopharmacol 1994;14:99–106
9. Khan A, Rudolph R, Baumel B, et al. Venlafaxine in depressed geriatric outpatients: an open-label clinical study. Psychopharmacol Bull 1995;31:753–758
10. Entsuah R, Upton GV, Rudolph R. Efficacy of venlafaxine treatment in depressed patients with psychomotor retardation or agitation: a meta-analysis. Hum Psychopharmacol 1995;10:195–200
11. Lecrubier Y, Bourin M, Moon CAL, et al. Efficacy of venlafaxine in depressive illness in general practice. Acta Psychiatr Scand 1997;95:485–493
12. Tylee A, Beaumont G, Bowden MW, et al. A double-blind, randomized, 12-week comparison study of the safety and efficacy of venlafaxine and fluoxetine in moderate to severe major depression in general practice. Primary Care Psychiatry 1997;3:51–58
13. Clerc GE, Ruimy P, Verdeau-Pailles J. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143
14. Guelfi JD, White C, Hackett D, et al. Effectiveness of venlafaxine in pa-

tients hospitalized for major depression and melancholia. J Clin Psychiatry 1995;56:450–458
15. Benkert O, Gründer G, Wetzel H, et al. A randomized, double-blind comparison of a rapidly escalating dose of venlafaxine and imipramine in inpatients with major depression and melancholia. J Psychiatr Res 1996;30: 441–451
16. Nierenberg AA, Feighner JP, Rudolph R, et al. Venlafaxine for treatment-resistant unipolar depression. J Clin Psychopharmacol 1994;14:419–423
17. Lecable P, Letzelter J-M, Lichtblau E, et al. An open-label study of the clinical acceptability of venlafaxine for depression. Primary Care Psychiatry 1995;1:119–125
18. Dierick M. An open-label evaluation of the long-term safety of oral venlafaxine in depressed elderly patients. Ann Clin Psychiatry 1996;8:169–178
19. Guy W. ECDEU Assessment Manual for Psychopharmacology. US Dept Health, Education, and Welfare publication (ADM) 76-338. Rockville, Md: National Institute of Mental Health; 1976:218–222
20. Zung WWK. A self-rating depression scale. Arch Gen Psychiatry 1965;12: 63–70
21. Danjou P, Hackett D. Safety and tolerance profile of venlafaxine. Int Clin Psychopharmacol 1995;10(suppl 2):15–20
22. Gonzalez Ruelas E, Diaz-Martinez A, Martinez Ruiz R, and the Venlafaxine Global Awareness Program Study Collaborative Group. An open assessment of the acceptability, efficacy, and tolerance of venlafaxine in usual care settings. Curr Ther Res 1997;58:609–630
23. Thompson C. Management of depression in real-life settings: knowledge gained from large-scale clinical trials. Int Clin Psychopharmacol 1994;9 (suppl 3):21–25
24. Duboff EA. Long-term treatment of major depressive disorder with paroxetine. J Clin Psychopharmacol 1993;13(suppl 2):28S–33S
25. Mesters P, Annsseau M, Brasseur R, et al. An open multicentre study to evaluate the efficacy and tolerance of fluoxetine 20 mg in depressed ambulatory patients. Acta Psychiatr Belg 1992;92:232–245

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