Once- Versus Twice-Daily Venlafaxine Therapy in Major Depression: A Randomized, Double-Blind Study

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Background: Psychotropic drug dosing regimens are often based on the pharmacokinetic elimination half-life of the compound. This implies that the pharmacokinetic half-life of the drug may be the critical or sole determinant of pharmacodynamic half-life. In the present study, we examined the safety and efficacy of once- versus twice-daily dosing regimens of the immediate-release formulation of venlafaxine, a serotonin and norepinephrine reuptake site blocker with a short elimination half-life.

Method: Forty-eight patients with a diagnosis of DSM-IV major depressive episode were randomly assigned to once-daily (N = 25) versus twice-daily (N = 23) venlafaxine. Venlafaxine was started at 37.5 mg daily with specified increments up to 225 mg daily. Efficacy was rated using the Hamilton Rating Scale for Depression (HAM-D), the Montgomery-Asberg Depression Rating Scale (MADRS), and the Clinical Global Impressions scale (CGI).

Results: Twenty-one patients in each group completed 6 weeks of treatment. We observed a significant reduction in mean weekly HAM-D and MADRS scores at weeks 1 through 6 for both dosing groups ($p < .001$). There were no statistically significant differences in mean HAM-D or MADRS scores between dosing groups at any time point. There was, however, a nonsignificant trend for a more rapid reduction in the mean HAM-D score at week 2 ($p < .06$) and in the mean MADRS score at week 1 ($p < .07$) and week 2 ($p < .09$) in the b.i.d. dosing group. Similarly, there was a significant decrease in the CGI score at week 2 ($p < .02$) in the b.i.d. dosing group. The rate of adverse events was similar between treatment groups; the most common adverse events were transient nausea and headaches.

Conclusion: These results indicate that the immediate-release formulation of venlafaxine may be safe and effective in some patients when used in a once-daily dose regimen. Moreover, the present results suggest that the short elimination half-life of immediate-release venlafaxine should not be the sole determinant for multiple daily dosing and that antidepressant activity may be more profoundly influenced by a drug's pharmacodynamic half-life than by its pharmacokinetic half-life.

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The efficacy of venlafaxine as a treatment for major depressive episode is well established. Several controlled clinical trials have found venlafaxine to be significantly superior to placebo at daily doses from 75 to 375 mg.[1–5] There is also emerging evidence that venlafaxine may have a more rapid onset of therapeutic action than placebo and tricyclic antidepressants.[6–8] While the delayed onset of antidepressant response with currently available antidepressants is well known,[9] a couple of studies with venlafaxine have suggested the possibility of an antidepressant response within the first 7 days of treatment.[2,8]

Venlafaxine has a relatively short mean ± SD elimination half-life of 5 ± 2 hours, while its active metabolite (*O*-desmethylvenlafaxine) has a mean half-life of 11 ± 2 hours. Most studies have recommended that the total daily dose of immediate-release formulation of venlafaxine be prescribed on a twice-daily (b.i.d.) or thrice-daily (t.i.d.) regimen for treating depression. While multiple daily dosing of venlafaxine may offer certain advantages, such as fewer dose-dependent side effects, there are also potential drawbacks, including reduced patient compliance.

Recently, our clinical experience has suggested that immediate-release venlafaxine can be administered once daily (q.d.) and that q.d. dosing might provide antidepressant efficacy similar to that observed with the currently recommended b.i.d. and t.i.d. dosing schedules. This observation raises the question: To what extent does the pharmacokinetic half-life of a drug (i.e., its dosing regimen) determine its pharmacodynamic half-life (i.e., antidepressant) activity?

In the present study, we examined the efficacy and safety of the immediate-release formulation of venlafaxine administered once-daily (q.d.) versus twice-daily (b.i.d.) in outpatients with a major depressive episode.

METHOD

Subjects

Forty-eight outpatients (31 women, 17 men) with a mean ± SD age of 43 ± 14 years were enrolled in the study. All subjects were recruited from the Depression Research Unit, University of Pennsylvania School of Medicine, Philadelphia, Pa., outpatient clinic or by self-referral. Subjects were not recruited by advertisement, and 5 patients had previously participated in clinical drug trials. All patients provided written informed consent in accordance with the ethical standards of the Institutional Review Board of the University of Pennsylvania. All patients were initially examined by a research psychiatrist using a semistructured diagnostic interview based on the Structured Clinical Interview for DSM-III-R (SCID) format,[10] and all fulfilled DSM-IV criteria[11] for major depressive episode. Patients with bipolar types II or not otherwise specified major depressive episode were included. All had moderate to severe depression with a pretreatment Hamilton Rating Scale for Depression (HAM-D)[12] score ≥ 20 on the 21-item HAM-D. Depressive symptoms had to have been present for at least 1 month prior to study entry. Table 1 displays demographic and clinical variables of the patient groups. There were no significant differences between dosing regimen groups.

Table 1. Demographic Features

Variable	Total (N = 48)	Venlafaxine q.d. (N = 25)	Venlafaxine b.i.d. (N = 23)	p Value
Age, y (mean ± SD)	43 ± 14	43 ± 13	42 ± 16	.48
Sex				
Male	17	9	8	
Female	31	16	15	.93
Diagnosis				
Unipolar	32	16	16	.77
Bipolar II and NOS	16	9	7	
Episode duration (wk)				
Mean ± SD	108 ± 218	90 ± 102	128 ± 300	.56
Median	27	52	26	.74
Episode chronicity				
≤ 2 y = acute	11	5	6	.62
> 2 y = chronic	37	20	17	
Melancholic features[a]				
Yes	16	9	7	
No	18	10	8	.71

[a]Data available from 34 patients.

Patients were excluded from the study if they demonstrated unstable medical disease. Patients with a history of hypertension that was stable on or off antihypertensive medication were included in the study. Subjects with a DSM-IV Axis I diagnosis other than major depressive episode, or those with a history of manic (i.e., bipolar I) disorder, schizophrenia, or refractory depression were excluded from the study.

At the time of the initial screen, all patients underwent a complete medical and psychiatric history and had the following procedures performed: a physical examination; blood pressure after sitting quietly at least 15 minutes and a blood pressure 1 to 2 minutes after standing; blood for hematologic and chemistry profiles including T_4, T_3-uptake, and thyrotropin levels; a urine analysis and urine drug screen; serum pregnancy test (in women of childbearing potential); and an electrocardiograph (ECG).

Procedures

After a 1-week single-blind, placebo lead-in period in which baseline HAM-D-21 scores remained ≥ 20 and reduction in the screen HAM-D score was less than 20%, eligible patients were randomly assigned to double-blind treatment with either q.d. or b.i.d. venlafaxine dosing regimens for up to 6 weeks. All subjects received their capsules on a b.i.d. schedule: (1) patients in the q.d. group received their entire venlafaxine dose in the morning and identical-appearing placebo capsules in the evening, while (2) patients in the b.i.d. group received one half their venlafaxine dose in the morning and one half in the evening. In this fashion, the q.d. group received 37.5-mg daily during week 1, 75 mg daily during week 2, 112.5 mg daily during week 3, and 150 mg to 225 mg daily during weeks 4 through 6. Members of the b.i.d. dosing group increased their daily venlafaxine dose slightly more rapidly, starting at 37.5 mg daily from days 1 to 3 and increasing to 37.5 mg b.i.d. during days 4 to 7. The 37.5-mg b.i.d. schedule was maintained during week 2 of treatment. The daily dose of venlafaxine was then increased to 112.5 mg daily during week 3, and maintained from 150 mg to 225 mg daily during weeks 4 through 6. Doses were increased as tolerated, based on clinical need, and never more rapidly than 75 mg every 4 days.

Efficacy measures were obtained at each visit (i.e., screen, baseline, days 7, 14, 21, 28, and 42) by a research psychiatrist using the HAM-D scale,[12] the Montgomery-Asberg Depression Rating scale (MADRS),[13] and the Clinical Global Impressions (CGI) scale.[14] Vital signs and weight were also obtained at each visit, while laboratory studies and ECG were repeated at the final (6-week) efficacy visit or at any point when medication was discontinued before week 6. Treatment-emergent adverse events were monitored by a research psychiatrist at baseline and study days 7, 14, 21, 28, and 42.

Concomitant chloral hydrate ≤ l000 mg at bedtime (or lorazepam ≤ 1.0 mg for patients allergic to chloral hydrate) was permitted for severe insomnia. Treatment with nonpsychotropic drugs for established, stable medical conditions (e.g., thyroid or estrogen hormone replacement, antihypertensive therapy) was permitted.

Statistical Methods

Efficacy analyses were used to examine data obtained from (1) patients who received active venlafaxine therapy

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Table 2. Scores on the 21-Item Hamilton Rating Scale for Depression During q.d. and b.i.d. Dosing*

A. Patients Treated for at Least 1 Week

		Baseline		Week 1[a,b]		Week 2[a,b]		Week 6 LOCF[a,b]	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	48	23.7	3.4	21.2	5.4	18.0	7.7	11.0	7.4
q.d.	25	24.4	3.6	22.8	5.2	20.6	6.5	12.6	7.5
b.i.d.	23	23.0	2.9	19.5	5.3	15.3	8.1	9.3	7.0

B. Patients Who Completed the 6-Week Study

		Baseline		Week 1[a]		Week 2[a]		Week 3[a]		Week 4[a]		Week 6[a,c]	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	42	23.6	3.4	21.2	5.6	17.7	7.8	14.2	7.0	11.7	6.8	9.6	6.4
q.d.	21	24.5	3.7	23.0	5.2	20.2	6.6	15.0	5.8	12.0	5.5	10.7	6.2
b.i.d.	21	22.6	2.8	19.4	5.5	15.2	8.2	13.4	8.0	11.5	8.0	8.6	6.7

*Abbreviations: b.i.d. = twice daily dosing, q.d. = once-daily dosing, LOCF = last observation carried forward.
[a]$p < .001$, ANOVA, representing change from baseline.
[b]Between-group difference: week 1, $p = .12$; week 2, $p = .06$; week 6, $p = .29$.
[c]Between-group difference: week 6, $p = .72$.

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for at least 1 week (i.e., 25 q.d. and 23 b.i.d. patients) and (2) patients who completed 42 days of double-blind therapy (i.e., 21 q.d. and 21 b.i.d. patients).

Demographic comparisons were conducted on the larger sample (N = 48) using a 1-way analysis of variance (ANOVA). When the averages for duration of illness suggested a difference between treatment groups, the medians were compared using the Wilcoxon rank sum test.

Efficacy data were initially examined using a general linear model that included baseline HAM-D or MADRS score as a covariate. For each evaluation period, the mean change from baseline was analyzed using a Student t test (to show the probability that the observed mean change was different from zero). A 1-way ANOVA with the Student t test was then used to compare the change in dosing regimen means at day 42.

Repeated measures ANOVA was performed using total HAM-D-21 and MADRS scores for each evaluation period including the baseline to compare the time trend patterns for each treatment group. This comparison is referred to as the time-by-treatment interaction using the Greenhouse-Geiser correction for correlated data.

Finally, categorical comparisons of demographic and efficacy data were examined using the chi-square test, with Yates correction where indicated for small sample size.

RESULTS

Efficacy

A total of 52 patients met study criteria for double-blind randomization: 26 q.d. and 26 b.i.d. patients. Of these subjects, 48 received double-blind venlafaxine for at least 1 week (25 q.d. and 23 b.i.d. patients) and 42 (21 q.d. and 21 b.i.d. patients) completed the entire 6-week trial.

Table 2A presents the mean ± SD total HAM-D-21 scores for patients who completed at least 1 week of double-blind treatment (N = 48). Table 2B displays mean HAM-D-21 for patients who completed the entire 6-week study (N = 42). We observed a nonsignificant trend toward a reduction in the mean HAM-D-21 score in the b.i.d. dosing group ($p < .06$) at week 2. However, a last-observation-carried-forward (LOCF) analysis demonstrated similar overall efficacy at week 6 in the q.d. and b.i.d. dosing groups ($p = .29$). Similarly, the change from baseline in mean HAM-D-21 scores for the entire patient sample was highly significant at each week ($p < .001$), while there was no between-group difference observed by week 6 ($p = .72$) (Table 2B).

Table 3A presents the mean total MADRS scores for patients who completed at least 1 week of double-blind treatment. We observed a nonsignificant trend toward a more rapid reduction in total MADRS scores in the b.i.d. dosing group than in the q.d. dosing group at week 1 ($p < .07$) and at week 2 ($p < .09$). Although this finding might support a more rapid onset of efficacy with b.i.d. dosing than with q.d. dosing, this group also had slightly more rapid dose titration. Moreover, a LOCF analysis showed similar overall efficacy by week 6 in the q.d. and b.i.d. dosing groups ($p = .21$).

The change versus baseline in mean MADRS scores for the entire patient sample was highly significant at each week ($p < .001$), while there was no between-group difference observed by week 6 ($p = .53$) (Table 3B).

Table 4 presents the change from baseline in the CGI scores for patients who completed at least 1 week of double-blind treatment. We observed significantly more patients in the b.i.d. group rated as either improved or very much improved at week 2 ($p < .02$). In contrast, a LOCF analysis found no group difference in CGI ratings by week 6 (p = NS).

Adverse Events

Table 5 presents results for 3 subsets of adverse events data. The most common side effects were nausea, ner-

Table 3. Scores on the Montgomery-Asberg Depression Rating Scale During q.d. and b.i.d. Dosing

A. Patients Treated for at Least 1 Week

		Baseline		Week 1[a,b]		Week 2[a,b]		Week 6 LOCF[a,b]	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	48	26.4	4.4	23.9	6.3	20.1	8.9	11.0	8.2
q.d.	25	27.0	5.0	25.6	6.0	22.5	8.1	12.6	8.5
b.i.d.	23	25.9	3.5	22.1	6.3	17.6	9.2	9.2	7.6

B. Patients Who Completed the 6-Week Study

		Baseline		Week 1[a]		Week 2[a]		Week 3[a]		Week 4[a]		Week 6[a,c]	
Group	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Total	42	26.5	4.2	24.0	6.4	19.9	9.2	16.3	8.7	12.5	8.0	9.4	7.1
q.d.	21	27.4	4.8	26.0	5.8	22.3	8.4	16.6	7.4	12.6	7.6	10.5	7.0
b.i.d.	21	25.5	3.4	22.0	6.6	17.5	9.6	16.1	10.1	12.4	8.5	8.3	7.2

[a]$p < .001$, ANOVA, representing change from baseline.
[b]Between-group difference: week 1, $p = .06$; week 2, $p = .09$; week 6, $p = .21$.
[c]Between-group difference: week 6, $p = .53$.

Table 4. Change From Baseline on Clinical Global Impressions Scale Ratings

A. Patients Treated For at Least 1 Week

	Week 1			Week 2			Week 6 (LOCF)[a]		
Degree of Change	Total (N = 48)	q.d. (N = 25)	b.i.d.[a] (N = 23)	Total (N = 48)	q.d. (N = 25)	b.i.d.[a] (N = 23)	Total (N = 48)	q.d. (N = 25)	b.i.d. (N = 23)
Improve 2+	1	0	1	7	1	6	24	13	11
Improve 1	11	4	7	16	7	9	16	7	9
No change	34	20	14	23	16	7	8	5	3
Worse	2	1	1	2	1	1	0	0	0

B. Patients Who Completed the 6-Week Study

	Week 1			Week 2			Week 3			Week 6[b]		
Degree of Change	Total (N = 42)	q.d. (N = 21)	b.i.d. (N = 21)	Total (N = 42)	q.d. (N = 21)	b.i.d. (N = 21)	Total (N = 42)	q.d. (N = 21)	b.i.d. (N = 21)	Total (N = 42)	q.d. (N = 21)	b.i.d. (N = 21)
Improve 2+	1	0	1	7	1	6	10	3	7	24	13	11
Improve 1	9	4	5	14	7	7	18	12	6	14	7	7
No change	30	16	14	19	12	7	13	5	8	4	1	3
Worse	2	1	1	2	1	1	1	1	0	0	0	0

[a]Between-group difference: week 1, $p = .18$; week 2, $p = .02$; week 6, $p = 1.00$.
[b]Between-group difference: week 6, $p = .50$.

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vousness, and headaches. The first 2 data sets include early events occurring from days 1 to 3 and from days 4 to 7 of double-blind treatment. Thus, adverse events occurring during these 2 periods were regarded as independent variables, so that patient counts during days 4 to 7 were regarded as independent from patient counts of days 1 to 3, i.e., as if they were completely new events not previously reported by the patient on days 1–3. The third group of adverse events represents those occurring during longer exposure to venlafaxine from days 15 to 42. There were no significant differences in adverse event rates or profiles between the dosing groups.

DISCUSSION

Results of this trial suggest that q.d. and b.i.d. dosing with the immediate-release formulation of venlafaxine may be effective and well tolerated in some depressed patients and that the use of a multiple daily dosing regimen may not be necessary to achieve a beneficial response. Moreover, several analyses suggest the possibility of a more rapid onset of therapeutic action favoring the b.i.d. dosing regimen, as reflected in the nonsignificantly lower HAM-D-21 ($p < .06$) and total MADRS scores ($p < .09$) at 2 weeks and in the significantly lower CGI scores ($p < .02$) at week 2. Furthermore, our data also suggest that initiating venlafaxine treatment at 37.5 mg daily and gradually increasing to 75 mg and to 225 mg daily (rather than starting at the currently recommended dosage of 75 mg daily) does contribute to a rapid, sustained therapeutic action from week 1 onward.[2,7,8]

Additionally, the present observations support the hypothesis that the elimination half-life should not be the sole determining factor influencing antidepressant dosing regimens. In this regard, several psychotropic drugs possessing a short elimination half-life are often prescribed on a q.d. basis. For example, tranylcypromine, with an elimination half-life of 1 hour, is often administered once daily.

Table 5. Patients (N = 52) Reporting 1 or More Adverse Event

	Dosing Regimen				
	q.d.		b.i.d.		
Interval	N	%	N	%	p Value
Early exposure					
Days 1 to 3 (new reports)					
Any patient reporting	18/26	69	17/26	65	.768
≥ 2 treatment related	17/26	65	16/26	62	.773
Days 4 to 7 (new reports)					
Any patient reporting	9/26	35	12/26	46	.397
≥ 2 treatment related	9/26	35	10/26	38	.773
Longer exposure (cumulative side effects)					
Days 15 to 42 (persistent and new reports)					
Any patient reporting	22/22	100	18/21	86	.108
≥ 2 treatment related	20/22	91	16/21	76	.240

Similarly, a double-blind efficacy comparison of q.d., b.i.d., and t.i.d. trazodone, a compound with an elimination half-life of 5 to 9 hours, demonstrated similar outcome among all dosing groups.[15] Therefore, it appears that the elimination half-life of some psychotropic drugs may not be the only critical factor in determining overall efficacy and safety and that other pharmacokinetic parameters (including rate of dose titration) and pharmacodynamic factors (like binding site affinity) may be more critical. Nevertheless, differences between the groups at certain time points and measures suggest that the half-life and dosing regimen do have impacts on drug effects.

The time course of antidepressant response is generally known to involve a significant delay. Although our study was not specifically designed to address rapidity of onset of therapeutic action, the finding of a significant reduction in total HAM-D and MADRS scores after only 1 week of venlafaxine treatment at a dose of 37.5 mg daily ($p < .001$) supports prior reports of a rapid onset of antidepressant activity with venlafaxine.[2,6–8] Differences seen between dosing groups on some efficacy measures during weeks 1 and 2 suggest the possibility that rapidity of onset may be enhanced by more frequent dosing. However, it must also be emphasized that, in the present study, the total daily dose of venlafaxine was more rapidly increased in the b.i.d. dosing group by 37.5 mg at days 4 to 7 of treatment.

Several caveats should be considered in the interpretation of the present results. For example, although maximum weekly dose increments were defined up to week 4 of treatment, venlafaxine doses were then prescribed as clinically warranted and as tolerated. Therefore, doses could be decreased, if warranted by side effects. Additionally, if patients did not require a maximum dose increase to 225 mg daily, they could be maintained at lower doses. It should, however, be emphasized that while the mean total daily venlafaxine doses were generally similar at each evaluation period in the q.d. and b.i.d. groups, the b.i.d. patients had a slightly more rapid dose titration at days 4 to 7 of the study. As noted, this more rapid titration in dose may have resulted in a more rapid improvement in clinical ratings at weeks 1 and 2 of treatment in the b.i.d. group. In contrast to earlier venlafaxine trials, the present study included patients with bipolar major depressive episode, and these patients may have responded to (or tolerated) venlafaxine differently from previously studied subjects with unipolar depression.

Other potential limitations of this study include the lack of a placebo control group, the limited sample size, and short treatment duration of the study.

Finally, the question of patient compliance is always an issue in an outpatient study of this type. To diminish the likelihood of noncompliance, daily dosing records were maintained and accurate pill counts were performed at each clinic visit.

In conclusion, we observed significant efficacy and mild side effects with the immediate-release formulation of venlafaxine administered on either a q.d. or b.i.d. dosing basis in this group of depressed outpatients. Although some of the statistical comparisons favored a more rapid onset of therapeutic action in the b.i.d. dosing group at weeks 1 and 2, LOCF analyses found both dosing regimens to be similar by week 6 of treatment.

Drug names: chloral hydrate (Noctec), lorazepam (Ativan and others), tranylcypromine (Parnate), trazodone (Desyrel and others), venlafaxine (Effexor).

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