



# **Wyeth Pharmaceuticals**

Excerpt From Canadian Supplemental New Drug Submission (December 1996)

Section 3.2.2.2.2

Venlafaxine Administration to Depressed Patients

Because the central effects of venlafaxine are preserved with the ER formulation, these observations suggest that the peaking of nausea severity before the  $t_{max}$  might involve a peripheral mechanism.<sup>2</sup> Further, although both venlafaxine formulations show similar AUCs, there was a reduced  $C_{max}$  and a delayed  $t_{max}$  for the ER formulation compared with the IR formulation. The results from healthy subjects support the hypothesis that the slope of increase of venlafaxine levels (plasma entry rate) contributes more to the severity of nausea than does the  $C_{max}$ .

Thus, the incidence of side effects, such as nausea, might be lessened with the use of an ER formulation of venlafaxine.

### 3.2.2.2.2 Venlafaxine Administration to Depressed Patients

#### 3.2.2.2.2.1 Design of Study 208

Study 208 was a multicenter, parallel-group, randomized, double-blind, placebo-controlled study in outpatients with major depression.<sup>3</sup> After a single-blind placebo study period, eligible patients were treated for a maximum of 12 weeks after which the study medication was tapered for 2 weeks.

The daily dosage schedule is shown in Table 3.2.2.2.1A:

Table 3.2.2.2.1A. DAILY DOSAGE SCHEDULE

Study Period	Venlafaxine ER (mg) (n = 97)	Venlafaxine IR (mg) (n = 96)
Days 1-14	75	75
Days 15-84	75 or 150	75 or 150
Taper week 1	0 or 75	0 or 75
Taper week 2	0	0

The dosage schedule allowed investigators to adjust the daily dose of venlafaxine in either formulation between 75 and 150 mg according to

tolerability and efficacy. The dose frequency was once daily for venlafaxine ER and twice daily (BID) for the IR formulation.

#### **3.2.2.2.2 Statistical Considerations**

Complementary analyses have been performed in addition to those previously described (see GMR-26165). The analyses were as follows:

##### **3.2.2.2.2.1 Study Drug Administration**

The mean daily dose for both venlafaxine formulations was defined as the average of the total daily doses for all patients at each time interval.

Adjusted mean doses were compared using a 1-way analysis of variance, and pairwise comparison between treatment groups was performed with an alpha level set at 0.05 (2-sided).

##### **3.2.2.2.2.2 Discontinuation Rate**

A survival curve was estimated according to the Kaplan-Meier method for discontinuations related to

- any reason
- AE
- failure to return

The survival curves between the treatment groups were compared using a log-rank test.

##### **3.2.2.2.2.3 Treatment-Emergent Nausea and Vomiting**

The presence of treatment-emergent nausea or vomiting was recorded at each time interval, independently of the start date. If a nausea or vomiting episode overlapped several time intervals, the event was counted in each interval.

Each instance of nausea or vomiting was assigned a severity score as follows:

- “0” for no nausea or vomiting
- “1” for mild nausea or vomiting
- “2” for moderate nausea or vomiting
- “3” for severe nausea or vomiting

An *index of severity* of nausea or vomiting for each time interval was determined by weighting each instance by a severity score and dividing by the total number of patients at that time interval.

A *cumulative severity index* was determined by adding the severity scores together and dividing by the total number of patients.

#### **3.2.2.2.2.4 Efficacy**

The variables analyzed were the HAM-D total (21 items) and the HAM-D anxiety-somatization factor (which included the “anxiety-psychic,” “anxiety-somatic,” “somatic gastrointestinal,” “somatic-general,” “hypochondriasis,” and “insight” items).

Efficacy evaluations were based on an intent-to-treat analysis, which included all randomly assigned patients with a baseline and at least 1 evaluation of at least 1 primary efficacy variable during the double-blind treatment phase or within 3 days of terminating treatment with the study drug. Data were analyzed with the LOCF method.

Adjusted mean changes in scores from baseline to endpoint were compared using analysis of covariance (ANCOVA) including treatment and center as factors in the model and the baseline score as a covariate. A Fisher F test was used to provide an overall test of efficacy. When the overall p-value was  $\leq 0.05$ , a pairwise comparison between treatment groups was performed, with an alpha level set at 0.05 (2-sided).

#### **3.2.2.2.2.3 Study Drug Administration**

The mean daily doses have been investigated for the active treatment groups at the different time intervals (Table 3.2.2.2.3A).

The mean daily dose of patients treated with venlafaxine ER was significantly higher than that for patients treated with venlafaxine IR at weeks 1, 4, 6, and 8 to 12. This suggests that the tolerability of venlafaxine ER was superior to that of venlafaxine IR, permitting the selection of higher doses.

TABLE 3.2.2.2.2.3A. MEAN DAILY DOSES OF VENLAFAXINE IR AND ER FORMULATION DURING THERAPY

Time Interval (days)	Mean Venlafaxine IR Dose (mg/day)	Mean Venlafaxine ER Dose (mg/day)	p-Value
1-7	70.7	73.6	0.0064
8-14	75.1	74.9	0.8562
15-21	113.6	123.6	0.0636
22-28	122.3	133.7	0.0282
29-35	124.6	134.3	0.0752
36-42	120.1	134.2	0.0109
43-49	123.5	133.7	0.0606
50-56	124.8	135.7	0.0404
57-63	121.7	139.6	0.0005
64-70	119.6	138.3	0.0009
71-77	121.9	136.2	0.0108
78-84	117.3	135.2	0.0016
> 84	82.6	89.4	0.1304

### 3.2.2.2.2.4 Safety Results

#### 3.2.2.2.2.4.1 Discontinuation Rates

Patients treated with venlafaxine ER had the lowest discontinuation rates for any reason (29%), as well as for most of the individually specified reasons. Table 3.2.2.2.2.4.1A summarizes the most frequent reasons for discontinuation.

sNDS Control #048954  
Vol. 23, P35

TABLE 3.2.2.2.4.1A. TOTAL NUMBER (%) OF PATIENTS WHO WITHDREW BY PRIMARY REASON

Reason	Placebo (n = 100)	Venlafaxine ER (n = 97)	Venlafaxine IR (n = 96)
<b>Any reason</b>	<b>41 (41)</b>	<b>28 (29)</b>	<b>38 (40)</b>
Adverse event	2 (2)	11 (11)	12 (13)
Unsatisfactory response	12 (12)	2 (2)	4 (4)
Failed to return	16 (16)	9 (9)	14 (15)

The survival curves comparison showed a trend for patients treated with venlafaxine IR to discontinue earlier than patients in the other treatment groups (Figure 3.2.2.2.4.1A). However, no significant difference was observed for discontinuation for “any reason” or “failed to return.”

A significant difference between placebo and the 2 formulations of venlafaxine was observed for discontinuation for “adverse event,” although there was no difference between the venlafaxine ER and IR formulations.

The time-course of discontinuation for any reason revealed different profiles (Figure 3.2.2.2.4.1B). For venlafaxine IR, the greatest number of patients (13) discontinued in the first week of treatment. The rate of discontinuation was more consistent over time and generally lower with venlafaxine ER than with the IR formulation. The maximal discontinuation rate with venlafaxine ER was also in the first week of treatment, but only 7 ER-treated patients discontinued (Figure 3.2.2.2.4.1B).

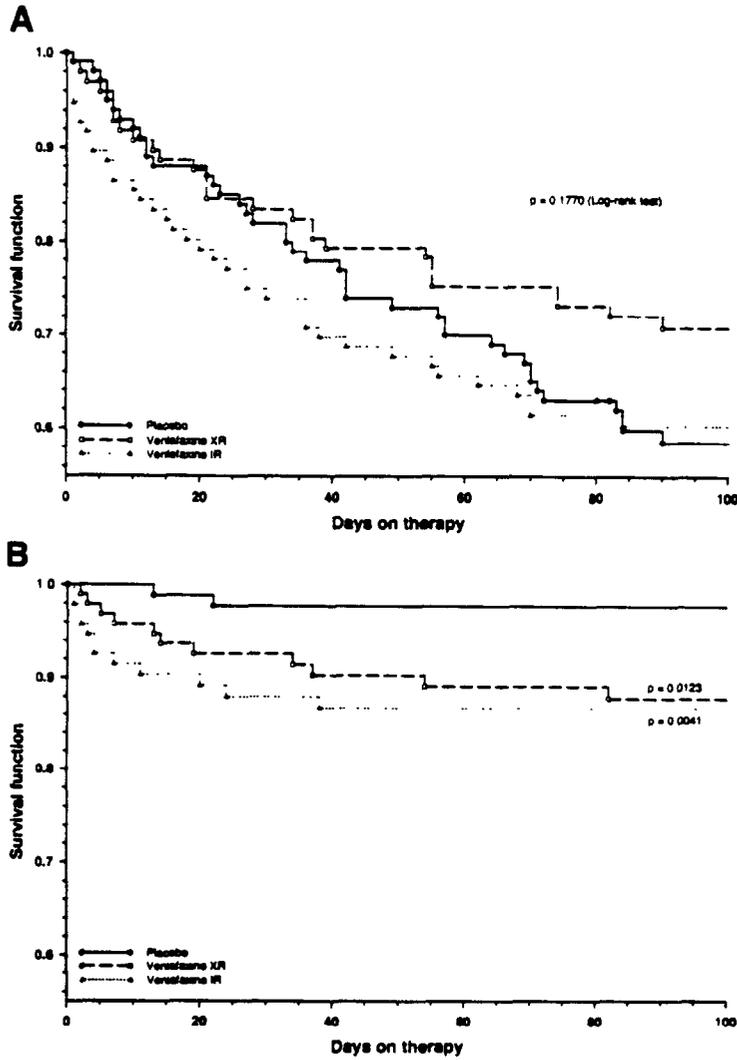
For patients who withdrew because of an AE, two-thirds (8 of 12) of the venlafaxine IR patients discontinued during the first week of therapy (Figure 3.2.2.2.4.1C). With venlafaxine ER, only one-third (4 of 11) did so during the first week.

Taken together, these observations suggest that the patients treated with venlafaxine ER were more likely to be treated for a longer time

sNDS Control #048954  
Vol. 23, P37

period, which in turn could increase the probability of response to the therapy.

FIGURE 3.2.2.2.4.1A. SURVIVAL CURVES FOR DISCONTINUATION FOR ANY REASON (A), ADVERSE EVENT (B) OR FAILED TO RETURN (C)



XR = Extended release formulation (ER)

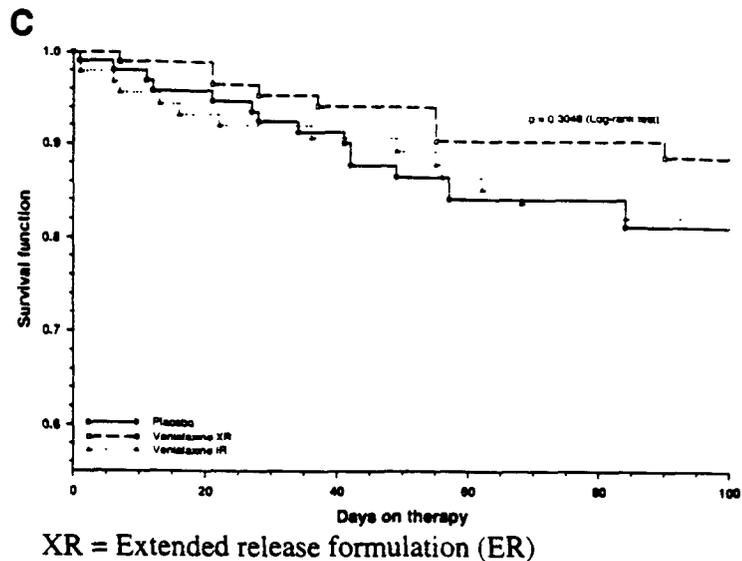
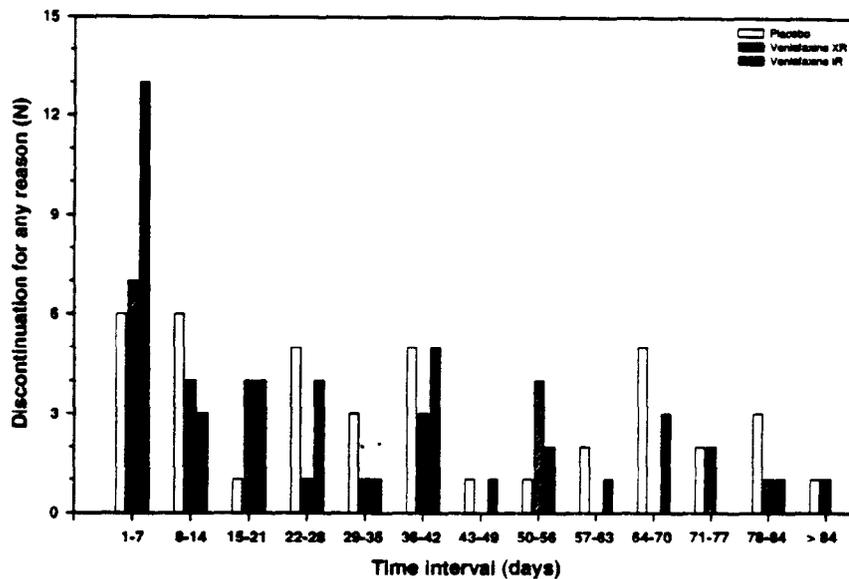
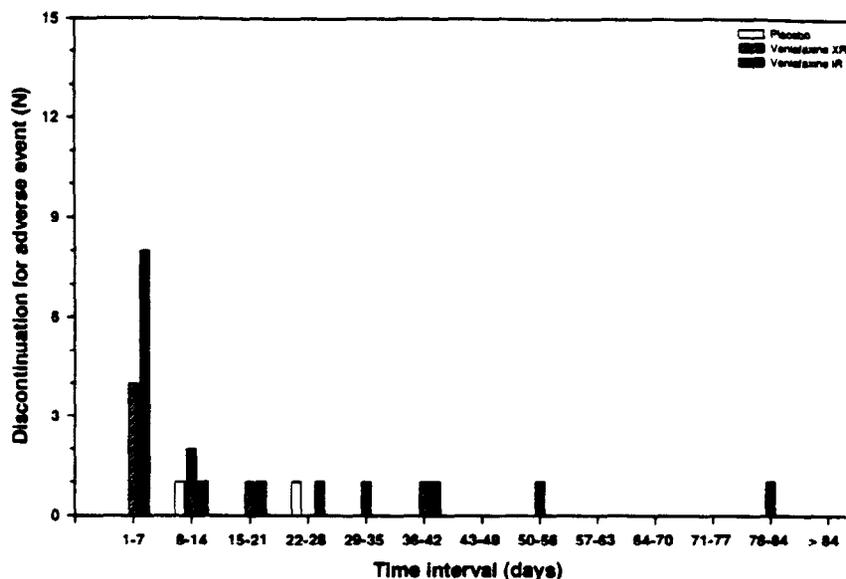


FIGURE 3.2.2.2.4.1B. NUMBER OF PATIENTS WHO DISCONTINUED OVER TIME FOR ANY REASON



XR = Extended release formulation (ER)

FIGURE 3.2.2.2.4.1C. NUMBER OF PATIENTS WHO DISCONTINUED FOR ANY ADVERSE REACTION



XR = Extended release formulation (ER)

3.2.2.2.4.2 Nausea

3.2.2.2.4.2.1 Incidence of Nausea

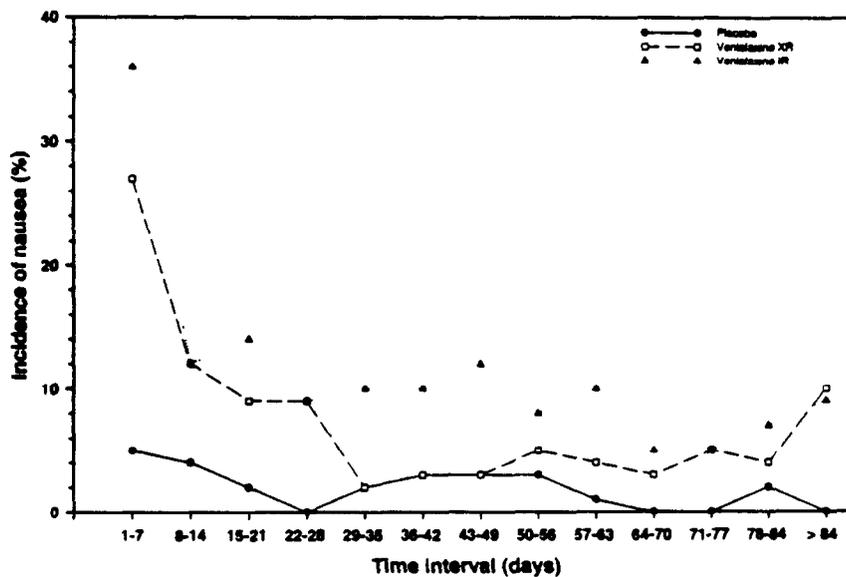
The same proportion of total number of patients reported nausea with venlafaxine ER and IR (45% in each group), and in each group, 3 patients discontinued due to nausea. However, the incidences over time were different. The incidence of nausea was numerically lower with venlafaxine ER than with IR at almost all time points (Table 3.2.2.2.4.2.1A and Figure 3.2.2.2.4.2.1A). If a nausea episode overlapped several time intervals, the event was counted in each interval. During the first week, 27% of patients reported nausea with venlafaxine ER compared with 36% with venlafaxine IR. The incidence of nausea with venlafaxine ER decreased markedly over time. After 4 weeks of treatment, the incidence of nausea with venlafaxine ER was equal to or below 5% and was then similar to the incidence with placebo. With the venlafaxine IR formulation, the

incidence remained higher, and approached or exceeded 10% during the first 9 weeks of treatment.

TABLE 3.2.2.2.4.2.1A. INCIDENCE OF TREATMENT-EMERGENT NAUSEA OVER TIME: NUMBER (%) OF PATIENTS

Time Interval (days)	n	Placebo	n	Venlafaxine ER	n	Venlafaxine IR
1-7	100	5 (5)	97	26 (27)	96	35 (36)
8-14	94	4 (4)	90	11 (12)	83	10 (12)
15-21	88	2 (2)	86	8 (9)	80	11 (14)
22-28	87	0 (0)	82	7 (9)	76	7 (9)
29-35	82	2 (2)	81	2 (2)	72	7 (10)
36-42	79	2 (3)	80	2 (3)	71	7 (10)
43-49	74	2 (3)	77	2 (3)	66	8 (12)
50-56	73	2 (3)	77	4 (5)	65	5 (8)
57-63	72	1 (1)	73	3 (4)	63	6 (10)
64-70	70	0 (0)	73	2 (3)	62	3 (5)
71-77	65	0 (0)	73	4 (5)	59	3 (5)
78-84	63	1 (2)	71	3 (4)	59	4 (7)
> 84	53	0 (0)	63	6 (10)	47	4 (9)

FIGURE 3.2.2.2.4.2.1A. INCIDENCE OF NAUSEA AS A TAEAE OVER TIME (PERCENTAGE OF PATIENTS)



XR = Extended release formulation (ER)

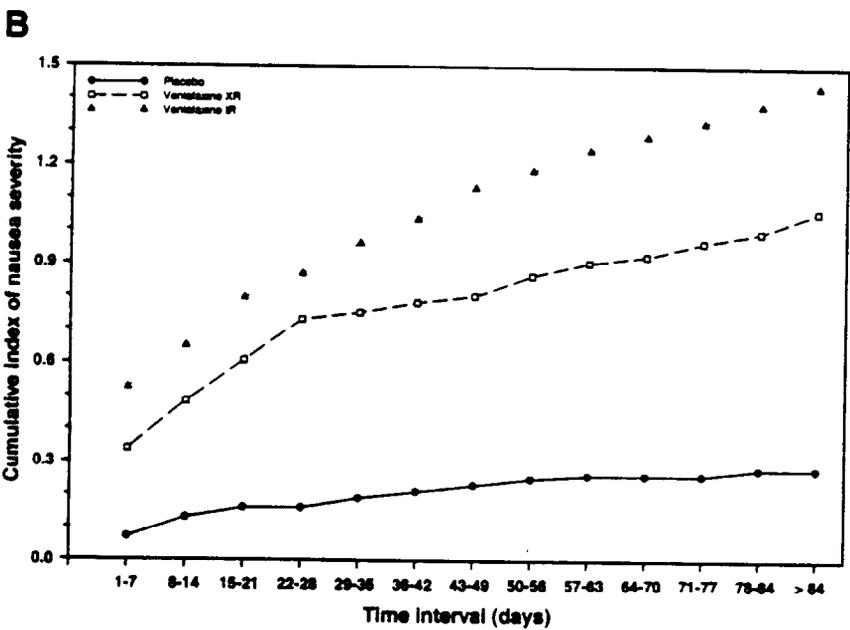
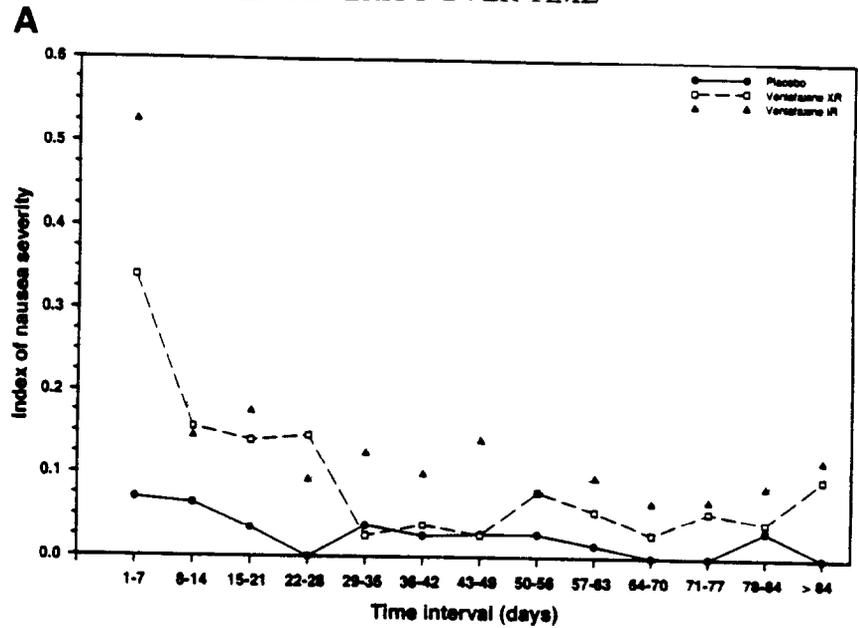
#### **3.2.2.2.4.2.2 Severity of Nausea**

The index of nausea severity (either crude, as defined by a severity score (section 3.2.2.2.2) or cumulative) integrated a rating of severity with the incidence of nausea in each treatment group (Figure 3.2.2.2.4.2.2).

The pattern of the crude severity index (Figure 3.2.2.2.4.2.2 part A) was similar to that of nausea incidence presented in Figure 3.2.2.2.4.2.1A. In the first week of therapy, patients treated with either venlafaxine formulations (ER and IR) showed more severe nausea when compared with placebo. The index of severity was strongly reduced beginning at the second week of therapy. However, the severity index for venlafaxine IR was higher than that for the ER formulation at all time points except the second and fourth weeks of treatment, when the trend was reversed. Further, the severity of nausea with venlafaxine ER was comparable to that with placebo at some time points starting from the fifth week of treatment.

The cumulative index of severity was markedly higher for venlafaxine (ER and IR) at all time points than for placebo (Figure 3.2.2.2.4.2.2 part B). The cumulative index of severity was also higher for venlafaxine IR compared with venlafaxine ER at all time points. The cumulative index increased linearly over the whole treatment period for venlafaxine IR, whereas after the first month, the increase in the cumulative index was less for venlafaxine ER.

FIGURE 3.2.2.2.4.2.2. CRUDE (A) AND CUMULATIVE (B) INDEX OF NAUSEA SEVERITY OVER TIME

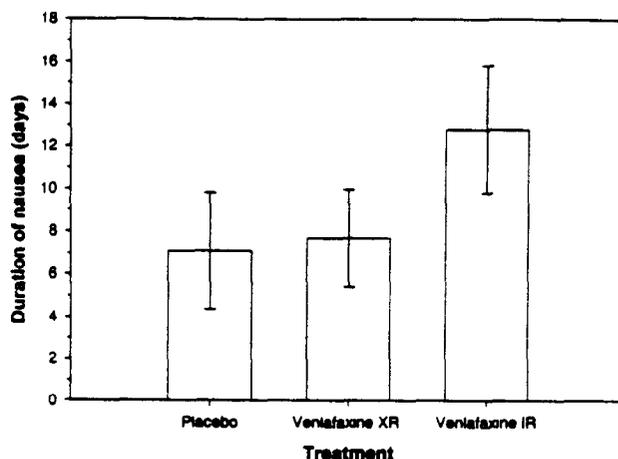


XR = Extended release formulation (ER)

**3.2.2.2.4.2.3 Duration of Nausea**

The mean duration of nausea with venlafaxine ER was similar to that determined for placebo (7.69 vs. 7.10 days, respectively; Figure 3.2.2.2.4.2.3A). The mean duration of nausea in the venlafaxine IR group (12.83 days) was higher than for the other 2 treatment groups. However, this difference did not reach the level of statistical significance ( $p = 0.3165$ ).

**FIGURE 3.2.2.2.4.2.3A. DURATION OF TREATMENT-EMERGENT NAUSEA (MEAN ± STANDARD ERROR)**



XR = Extended release formulation (ER)

**3.2.2.2.4.2.4 Outcomes of Patients With Nausea**

Among the population of patients who experienced nausea, patient outcomes were determined for each of the treatment groups (Table 3.2.2.2.4.2.4A).

sNDS Control #048954  
Vol. 23, P43 and  
Supportive Tables

TABLE 3.2.2.2.4.2.4A. OUTCOMES OF PATIENTS WHO REPORTED NAUSEA AT ANY TIME:  
NUMBER (%) OF PATIENTS

Treatment Group	Number of Patients With Nausea	Number (%) of Patients With Nausea Who Completed	Number (%) of Patients With Nausea Who Discontinued for the Reason of				
			Any	AE	FR	PV	LE
Placebo (n = 100)	10	3 (30)	7 (70)	0	2	1	4
Venlafaxine IR (n = 96)	43	28 (65)	15 (35)	7	7 <sup>a</sup>	1	0
Venlafaxine ER (n = 97)	44	38 (86)	6 (14)	4	1	1	0

Abbreviation: AE = adverse event; FR = failed to return; LE = lack of efficacy; PV = protocol violation  
a: One (1) patient had a primary reason of discontinuation labeled "patient request," as the patient felt he was taking too many pills. This single patient was classified as "failed to return" for this analysis.

Overall, patients who experienced nausea were marginally more likely to complete the study when they were treated with venlafaxine ER than when they were treated with venlafaxine IR (86% vs. 65%, respectively; Fisher's exact test,  $p = 0.056$ ). In addition, significantly ( $p = 0.046$ ) more patients who discontinued for AEs or failure to return were in the venlafaxine IR group (14 patients) than in the venlafaxine ER group (5 patients; Fisher's exact test). These results suggest that the nausea experienced by patients receiving venlafaxine ER was less severe than that experienced by patients receiving venlafaxine IR.

### 3.2.2.2.4.3 Vomiting

#### 3.2.2.2.4.3.1 Incidence of Vomiting

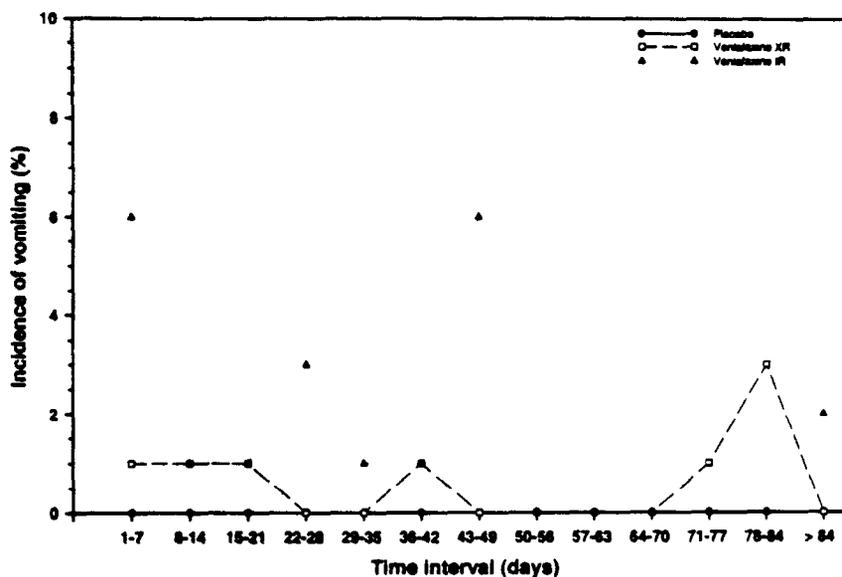
There was a marked difference in the number of patients who experienced treatment-emergent vomiting during the study:

- 5 venlafaxine ER-treated patients (5%) experienced vomiting, in 3 of whom it was considered related to study treatment.
- 16 venlafaxine IR-treated patients (17%) experienced vomiting, in 15 of whom it was considered related to study treatment.
- No patients in the placebo group experienced treatment-emergent vomiting.

sNDS Control #048954  
Vol. 23, P70

Over time (Figure 3.2.2.2.4.3.1A), the incidence of vomiting with venlafaxine ER was low, with 1% of patients experiencing vomiting each week during the first 3 weeks of treatment. One percent (1%) of patients experienced vomiting during the sixth week of therapy, and 3% experienced vomiting after 3 months. With venlafaxine IR (Figure 3.2.2.2.4.3.1A), 6% of patients experienced vomiting in the first week of treatment; 6% also experienced vomiting in the seventh week. The incidence of vomiting was numerically higher with venlafaxine IR than with venlafaxine ER in the first 2 months of therapy.

FIGURE 3.2.2.2.4.3.1A. INCIDENCE OF VOMITING AS A TAE OVER TIME (PERCENTAGE OF PATIENTS)



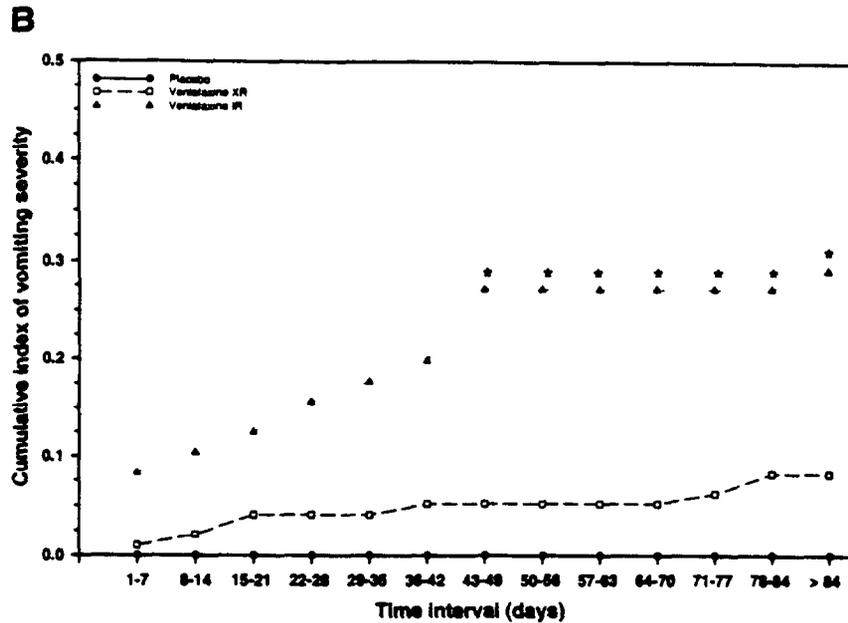
XR = Extended release formulation (ER)

### 3.2.2.2.4.3.2 Severity of Vomiting

The index of vomiting severity (either crude or cumulative) integrated a rating of severity with the incidence of vomiting in each treatment group (Figure 3.2.2.2.4.3.2A).

The pattern of the crude severity index was similar to the one for nausea incidence presented in Figure 3.2.2.2.4.3.1A. The index of vomiting severity was higher with venlafaxine IR than with venlafaxine ER during the first 2 months of treatment (Figure 3.2.2.2.4.3.2A). With venlafaxine ER, the index of vomiting severity was fairly stable during the treatment period. Further, the cumulative index of severity for venlafaxine ER showed a relatively flat pattern, with small stage of increase. With venlafaxine IR, the cumulative index of severity increased constantly during the first 2 months, thereafter reaching a plateau. Moreover, the cumulative index of vomiting severity was significantly ( $p<0.05$ ) higher with venlafaxine IR than with venlafaxine ER from week 7 (days 43 to 49) onward.

FIGURE 3.2.2.2.4.3.2A. CUMULATIVE INDEX OF VOMITING SEVERITY OVER TIME



\*  $p \leq 0.05$  compared with venlafaxine IR.  
 XR = Extended release formulation (ER)

**3.2.2.2.4.3.3 Duration of Vomiting**

The mean duration of vomiting was similar for the 2 venlafaxine formulations. The mean duration was 2.20 and 1.79 days for the ER and IR formulations, respectively. There was no difference between the groups ( $p = 0.6391$ ).

**3.2.2.2.4.3.4 Outcomes of Patients With Vomiting**

The outcomes of patients who experienced vomiting during the study were analyzed for the different treatment groups (Table 3.2.2.2.4.3.4A).

sNDS Control #048954  
 Vol. 23, P43 and  
 Supportive Tables

TABLE 3.2.2.2.2.4.3.4A. OUTCOMES OF PATIENTS WHO REPORTED VOMITING AT ANY TIME:  
NUMBER (%) OF PATIENTS

Treatment Group	Number of Patients With Vomiting	Number (%) of Patients Who Completed	Number (%) of Patients Who Discontinued for the Reason of			
			Any	AE	FR	Other
Venlafaxine IR (n = 96)	16	11 (69)	5 (31)	3	1	1
Venlafaxine ER (n = 97)	5	4 (80)	1 (20)	1	0	0

Abbreviation: AE = adverse event; FR = failed to return; Other = other event

Patients experiencing vomiting and treated with venlafaxine ER tended to have a greater probability of completing the study than patients treated with venlafaxine IR (80% vs 69%, respectively), although the small number of observations did not allow demonstration of a statistically significant difference (Fischer's exact test,  $p=0.596$ ).

### 3.2.2.2.2.5 Efficacy Results

#### 3.2.2.2.2.5.1 HAM-D Total and Depressed Mood Item

Both venlafaxine formulations demonstrated superiority to placebo for the change in HAM-D total score, at week 2 and from weeks 4 through 12 (Figure 3.2.2.2.2.5.1A). The change in HAM-D total score at week 12 was about 15 points for venlafaxine ER, 12 points for venlafaxine IR, and 9 points for placebo.

The comparison of the ER and IR formulations showed a significant advantage for venlafaxine ER compared with venlafaxine IR at week 8. This difference was maintained at week 12 (Figure 3.2.2.2.2.5.1A).

For the HAM-D depressed mood item, venlafaxine ER was significantly superior to placebo starting at week 2 through week 12 (Figure 3.2.2.2.2.5.1B). With venlafaxine IR, a significant superiority was also observed at week 2, and continuing starting at week 4 until

sNDS Control #048954  
Vol. 23, P45s