Effects of Venlafaxine on Blood Pressure: A Meta-Analysis of Original Data From 3744 Depressed Patients

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Background: Venlafaxine hydrochloride, a structurally novel antidepressant, is also the first nontricyclic serotonin/norepinephrine reuptake inhibitor. Although venlafaxine has an overall side effect and safety profile that is comparable to other newer antidepressants, it can cause both transient and sustained elevations of supine diastolic blood pressure (SDBP), probably the result of noradrenergic potentiation.

Method: Presented here is a meta-analysis of original data on blood pressure, using both random effects and a multivariate survival analyses. The sample consisted of 3744 patients with major depression who were studied in controlled clinical trials comparing venlafaxine with imipramine and/or placebo. Patients were treated for 6 weeks of acute phase therapy; some responders received up to 1 year of continuation phase therapy.

Results: Venlafaxine and imipramine were associated with small, but statistically significant, increases in SDBP during acute phase therapy. When compared with imipramine and placebo, venlafaxine was also associated with a greater proportion of persistent elevations of SDBP during continuation therapy. The effect of venlafaxine was highly dose dependent, and the incidence of elevated SDBP was statistically and clinically significant only at dosages above 300 mg/day. Venlafaxine did not adversely affect the control of blood pressure for patients with preexisting high blood pressure or elevated baseline values.

Conclusion: Venlafaxine has a dose-dependent effect on SDBP that is clinically significant at high dosages. Concern about blood pressure effects should not deter first-line use of this effective antidepressant, although more extensive studies of patients with cardiovascular diseases are still necessary.

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Venlafaxine hydrochloride, a structurally novel phenylethylamine compound, was approved in 1993 by the U.S. Food and Drug Administration (FDA) for treatment of depression. Like several of the tricyclic antidepressants (TCAs), venlafaxine is a serotonin/norepinephrine reuptake inhibitor (SNRI).[1] Unlike the TCAs, however, venlafaxine has little affinity for α_1-adrenergic, histaminergic, or muscarinic receptors.[1] Available clinical evidence suggests that venlafaxine may share the relative safety of the selective serotonin reuptake inhibitors (SSRIs) with respect to overdosage and incidence of orthostatic hypotension and cardiotoxicity.[2] A once-daily extended-release (XR) formulation that recently became available will enhance patient compliance. In addition, it was shown in one study to have the same safety, efficacy, and tolerability as the standard (immediate-release) venlafaxine formulation,[3] while in another study the XR formulation demonstrated superior efficacy and tolerability.[4]

The unique profile of venlafaxine may offer particular promise for treatment of melancholia and other severe depressive states, for which there is considerable evidence of dysfunction of both noradrenergic and serotonergic neurotransmission.[5,6] Moreover, persistent doubts exist concerning the efficacy of the SSRIs in such severe depressive states,[7,8] and comparative studies have yielded mixed results.[9–12] To date, venlafaxine and the SSRI fluoxetine have been compared in 2 published trials[13,14]; the results of both studies suggest that venlafaxine (in doses of 150 to 375 mg/day) may be more effective than fluoxetine (in doses of 20 to 60 mg/day).

One common concern about first-line use of venlafaxine is the risk of increased blood pressure.[1,2] In order to better characterize this effect, a meta-analysis of the blood pressure data of 3744 patients with a diagnosis of major depression was conducted. These patients were treated in randomized, double-blind phase 2 and phase 3 clinical trials comparing venlafaxine (N = 2817) with placebo (N = 607) or imipramine hydrochloride (N = 320). Beyond examining the effects of these treatments on blood pressure, the aims of this meta-analysis included determining dose-response relationships and identifying specific subgroups of depressed patients at greater risk for development of treatment-emergent blood pressure elevations.

Table 1. Summary of Patient Characteristics

Variable	Venlafaxine (N = 2817) N	%	Imipramine (N = 320) N	%	Placebo (N = 607) N	%
Sex						
Female	1745	62	198	62	362	60
Male	1072	38	122	38	245	40
Treatment setting						
Outpatient	2613	93	238	74	498	82
Inpatient	204	7	82	26	109	18
Age, y						
< 40	1042	37	146	46	285	47
40–64	1420	50	159	50	292	48
≥ 65	355	13	15	5	30	5
	Mean	SD	Mean	SD	Mean	SD
SDBP values, mm Hg						
Baseline	77.8	9.4	76.7	9.4	75.5	8.9
Endpoint (acute)	78.8	10.2	75.0	9.7	75.0	9.7
Δ SDBP	1.2	8.9	1.0	8.2	–1.5	8.1
Δ % SDBP	2.1	11.9	1.9	10.9	–1.6	10.5

Abbreviation: SDBP = supine diastolic blood pressure.

METHOD

Subjects

Entry into the clinical trials included herein required that the patients (1) meet Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised (DSM-III-R) criteria[15] for a current, principal diagnosis of major depression; (2) score at least 20 on the 21-item Hamilton Rating Scale for Depression[16]; (3) have no poorly controlled or serious medical illness; and (4) provide explicit written informed consent. Psychiatric diagnosis was typically determined by the principal investigator at each site according to a criteria checklist. Patients' medical histories and eligibility were confirmed by a complete physical examination, appropriate blood work, and a 12-lead electrocardiogram.

Patients were enrolled in 21 outpatient and 6 inpatient clinical trials, involving 180 different sites. The number of patients per site per study ranged from 10 to 427, although only a single site had a number of participants that was in the hundreds. Pretreatment patient characteristics are summarized in Table 1.

Study Drugs

Venlafaxine, imipramine, and placebo were prescribed in identical capsules. Dosages of venlafaxine ranged from 25 mg/day to 375 mg/day. The numbers of patients treated at various dosages of venlafaxine were as follows: ≤ 100 mg/day, N = 898; 101 to 200 mg/day, N = 1243; 201 to 300 mg/day, N = 479; and > 300 mg/day, N = 186. The exact protocol dosage could not be determined for 11 patients because of missing data. Total daily dosages of imipramine ranged from 75 mg/day to 225 mg/day.

All studies provided at least 6 weeks of acute phase therapy. Several studies also included FDA-approved 12-month double-blind extension protocols.

Measurement of Blood Pressure

Blood pressure was measured at each visit (i.e., weekly during acute phase therapy and monthly during continuation therapy) using a standard protocol.[17] Patients were instructed to lie supine on an examination table in a quiet, private room for 5 minutes before systolic and diastolic blood pressures were measured with a mercury sphygmomanometer, an appropriately sized cuff, and a stethoscope. Next, orthostatic blood pressure measurements were taken at 1 and 3 minutes after standing.

Blood pressure readings obtained in this manner correlate highly with direct intra-arterial measurements.[18] The interrater reliability of such measurements is also quite high (i.e., correlations of > 0.9).[17,18] The actual readings obtained vary considerably, however, both within and across sessions, and differences of 5, 10, or even 15 mm Hg between assessments are not uncommon.[19] For example, blood pressure readings are typically higher when measured at the beginning of visits, and higher readings tend to decrease when measured across multiple visits.[17–20] Although isolated elevations of blood pressure may have some prognostic value, readings that are observed repeatedly over time are more valid. The Fifth Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V)[20] recommends that a new diagnosis of hypertension should not be made until an elevated reading has been confirmed on at least 2 subsequent occasions.

Blood pressure values in the general population are distributed normally and should be analyzed as a continuous variable.[20] However, hypertension is a disease and traditionally has been classified categorically. In the JNC V,[20] for example, sustained elevations of supine systolic blood pressures of 140 mm Hg or supine diastolic blood pressures of ≥ 90 mm Hg are considered categorically abnormal and warrant treatment. For the purposes of this report, supine diastolic blood pressure (SDBP) was analyzed as a representative continuous measure and the JNC V definition was chosen as the primary categorical outcome of interest. This definition may be considered by some to be too conservative and, therefore, the number of cases with any increase in SDBP resulting in an acute phase endpoint value of ≥ 90 mm Hg also was determined.

Statistical Methods

The original data for the statistical analysis were provided by Wyeth-Ayerst Laboratories. In working with such a data set, the loss of informative cases as a result of attrition is an endemic problem, and the method of handling this problem can have marked effects on results.[21] This is particularly true when attrition is the result of a nonrandom factor, such as differences in efficacy or adverse effects. The intent-to-treat strategy is often used to retain as many data as possible, with the last available assessment used as a termination or end point score.[21] In the

case of analyses of repeated measurements, the last observation carried forward (LOCF) method is commonly used to account for the missing data. Alternatively, completers-only analyses may be used to focus on the subjects who have a complete data set at a selected time. Obviously, neither method is fully satisfactory. The first implies that dropouts have static values over time, whereas the second ignores the dropouts altogether.[21,22] In the current analyses, for example, the LOCF approach would introduce bias by imputing that a patient who dropped out with a single elevated reading had a sustained increase in blood pressure. Conversely, a completers-only analysis would exclude the data of patients withdrawn because of elevated blood pressure.

More recently, statistical methods have been introduced to lessen the effect of attrition on longitudinal data sets. For continuous data, such as SDBP recordings, the random-effects model with repeated measures[22] is a useful method that retains all available data while minimizing the imputation bias of the LOCF method. For categorical data, such as the incidence of cases of elevated blood pressure, survival (life table) analysis serves a similar role, with dropouts censored from longitudinal analysis at the point of attrition. The Cox proportional hazards model[23] of survival analysis enables the effect of potentially interactive covariates or risk factors to be studied. In the case of blood pressure research, patient age and sex are potentially informative covariates that also should be taken into account.[21] Both the random-effects and Cox proportional hazards models permit the use of covariates and were chosen for this meta-analysis.

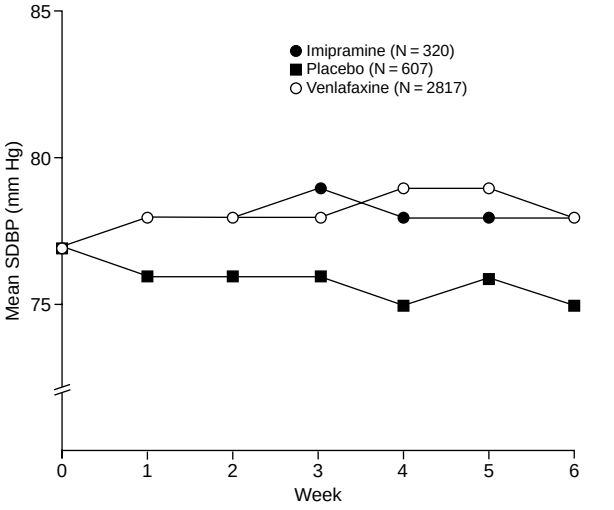
Two sets of statistical tests were performed. The first dealt specifically with blood pressure changes across the first 6 weekly visits. The second set of analyses focused on the subset of patients who received up to 12 months of continuation phase therapy.

RESULTS

Effects on Supine Diastolic Blood Pressure

Acute phase therapy. Figure 1 shows the least squares mean SDBP readings for the 3 treatment groups during the 6 weeks of treatment. The random-effects model analysis revealed significant effects for drug ($F = 12.48$, $df = 2, 21 \times 10^3$; $p < .001$) and the time × drug term ($F = 3.47$; $df = 3, 21 \times 10^3$; $p < .15$). Age and sex also were significant as covariates (both p values were < .001); specifically, older patients and men had larger increases in SDBP. Post hoc analyses indicated that the main and interaction effects were due to increases in mean SDBP in both the venlafaxine and imipramine groups relative to the placebo group ($p < .05$). The magnitude of these differences between the active drugs and placebo was quite small, however. For example, the mean increase in SDBP in the venlafaxine group was 1.02 mm Hg. Posttreatment SDBP values were strongly correlated with pretreatment values, and this relationship was remarkably consistent across medications (venlafaxine, $r = 0.63$; imipramine, $r = 0.64$; placebo, $r = 0.62$).

Figure 1. Adjusted Mean Supine Diastolic Blood Pressure (SDBP) During Acute Phase Therapy



Continuation phase therapy. Six hundred four patients enrolled in extension protocols following acute phase therapy and were treated with placebo (N = 106), venlafaxine (N = 418), or imipramine (N = 80). After taking into account the covariates (i.e., age, sex, and SDBP values at week 6), the main effect for drug was not significant (drug: $F = 0.55$, $df = 2, 16 \times 10^3$; $p = .58$). There was, however, a significant effect for time × drug ($F = 2.83$, $df = 3, 16 \times 10^3$; $p = .037$). This reflected that blood pressure values decreased during continued therapy with placebo and venlafaxine, but not with imipramine. The slope estimates for these effects were as follows: venlafaxine, –0.04, $p = .073$; imipramine, +0.12, $p = .25$; and placebo, –0.17, $p = .048$.

Incidence of Sustained Elevation of Supine Diastolic Blood Pressure

Acute phase therapy. A sustained elevation in SDBP was observed with the following crude incidences: venlafaxine, 4.8% (135/2817); imipramine, 4.7% (15/319); and placebo, 2.1% (13/605) ($\chi^2 = 8.45$, $df = 2$, $p = .015$). The incidence of sustained elevated SDBP was not statistically significant after adjustment for age and sex (log rank $\chi^2 = 4.91$, $df = 2$, $p = .086$), although both venlafaxine ($p = .037$) and imipramine ($p = .039$) groups had significantly higher rates than the placebo group on pairwise contrasts.

A second analysis was performed to assess the risk of simply "crossing over" the 90 mm Hg SDBP categorical boundary at week 6 or endpoint, irrespective of the mag-

Table 2. Incidence of SDBP Values of 90 mm Hg or Higher at Endpoint

SDBP ≥ 90 mm Hg at Endpoint	Venlafaxine (N = 2495)		Imipramine (N = 291)		Placebo (N = 558)	
	N	%	N	%	N	%
Yes	286	11.5[a]	23	7.9[b]	32	5.7[c]
No	2209	88.5	268	92.1	526	94.3

[a]p < .001 for venlafaxine vs. imipramine.
[b]p = .24 for imipramine vs. placebo.
[c]p < .001 for venlafaxine vs. placebo.

nitude of increase. These results are summarized in Table 2. The incidence of SDBP values ≥ 90 mm Hg at endpoint was: venlafaxine, 11.5% (286/2495); imipramine, 7.9% (23/291); and placebo, 5.7% (32/558). The incidence of elevated SDBP using this less restrictive definition was significantly higher in the venlafaxine condition as compared to either placebo or imipramine (p < .001, Fisher's exact test). After excluding the cases that met the JNC V[20] definition, the incidence of "subsyndromal" blood pressure elevation was as follows: venlafaxine, 5.4% (135/2495); imipramine, 27% (8/291); and placebo 3.4% (19/558) ($\chi^2 = 7.02$, df = 2, p = .030).

Continuation phase therapy. A total of 467 patients entered the continuation phase with normal SDBPs; this subgroup included a reasonably large number of patients treated with venlafaxine (N = 309), but a relatively smaller number of patients treated with imipramine (N = 65) or placebo (N = 93). Although only 21 patients (4.5%) developed elevated SDBP during this phase, the incidence was significantly higher in the venlafaxine group (log rank $\chi^2 = 5.98$, df = 2, p = .0503).

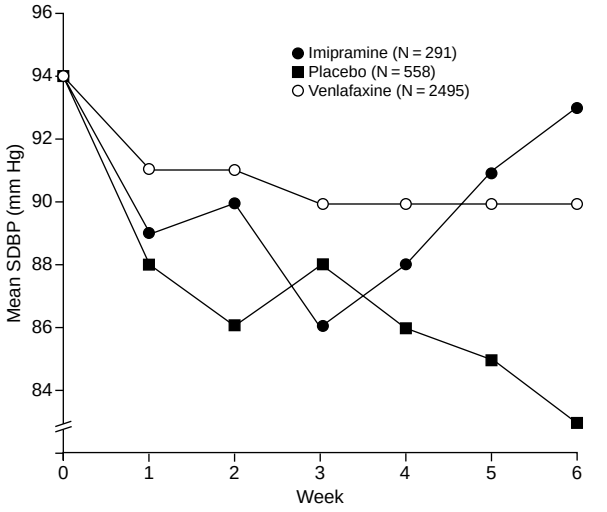
Persistence of Elevated Supine Diastolic Blood Pressure

One hundred thirty-seven patients entered the continuation phase with sustained elevated SDBP values (venlafaxine, N = 109; imipramine, N = 15; placebo, N = 13). Among the venlafaxine-treated patients, 51% (N = 56) continued to meet criteria for elevated SDBP as compared with 27% (N = 4) of imipramine-treated patients and 23% (N = 3) of placebo-treated patients. This trend did not reach statistical significance in the small sample ($\chi^2 = 4.70$, df = 2, p = .095).

Effects of Treatment as a Function of Pretreatment Blood Pressure

A total of 390 patients began acute phase therapy with elevated SDBP (venlafaxine, N = 349; imipramine, N = 18; placebo, N = 23). The random-effects model documented a significant time × drug interaction effect (F = 3.23, df = 3, 1383; p = .02), whereas the effect for drug was not significant (F = 1.47, df = 2, 1383; p = .23). Depressed patients with elevated pretreatment SDBP values had reductions of blood pressure during treatment

Figure 2. Adjusted Mean Supine Diastolic Blood Pressure (SDBP) During Acute Phase Therapy for Patients With Elevated Baseline SDBP Values (≥ 90 mm Hg)



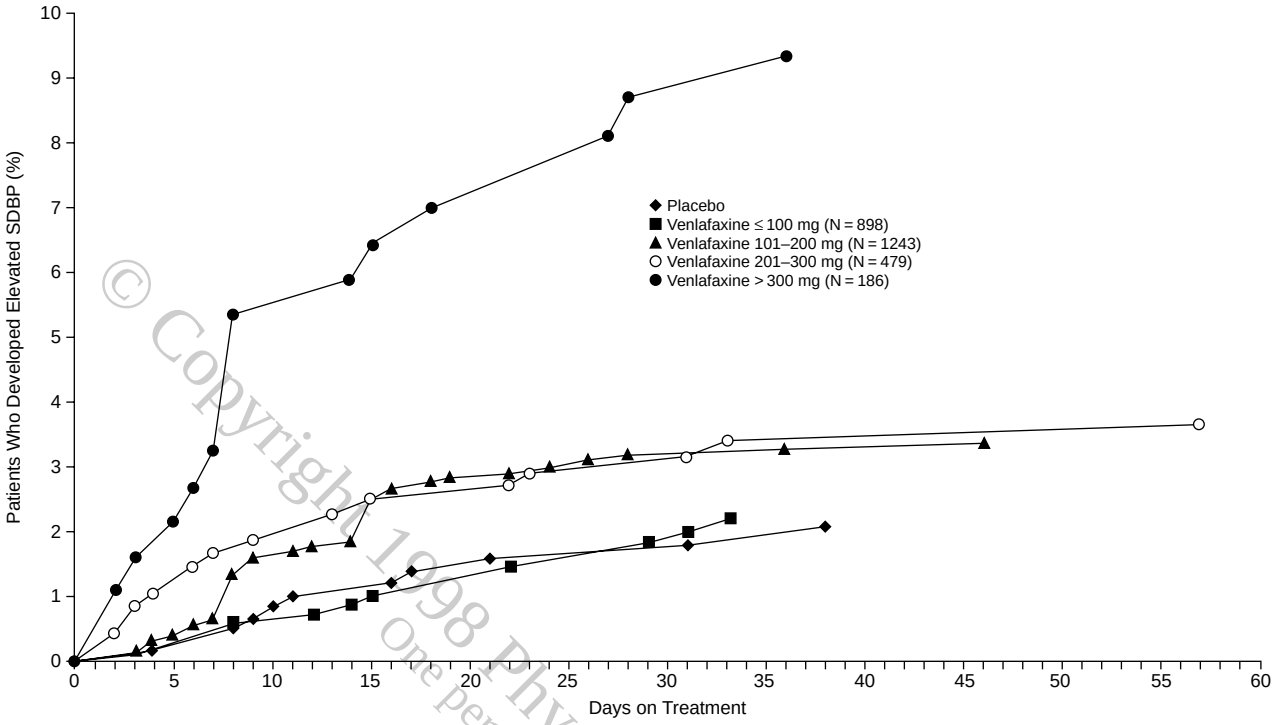
with either venlafaxine (t = –2.17, df = 1383, p = .030) or placebo (t = –2.19, df = 1383, p = .028), but not with imipramine (t = 0.39, df = 1383, p = .70). Imipramine pharmacotherapy had a biphasic effect on SDBP, reflected by an initial reduction followed by increased values after the third week of pharmacotherapy (Figure 2).

One hundred forty patients (venlafaxine, N = 82; imipramine, N = 13; placebo, N = 45) with a history of hypertension entered treatment taking stable dosages of antihypertensives. When compared with the remainder of the study group, these patients had significantly higher baseline SDBP values: 83.7 (SD = 8.9) mm Hg vs. 77.2 (SD = 9.2) mm Hg; (F = 67.3, df = 1, 3728; p < .001). The random-effects model analysis documented a significant effect for drug (F = 15.3, df = 2, 136; p < .001), although the drug × time interaction effect was not significant (F = 1.18, df = 54, 822; p = .186). The adjusted least squares means ± SE for the 3 treatment groups at the end of acute phase therapy were as follows: venlafaxine, 85.5 ± 0.6 mm Hg; imipramine, 84.3 ± 1.3 mm Hg; and placebo, 80.2 ± 0.8 mm Hg. Patients treated with placebo had a significant reduction in SDBP values (p < .01), whereas both active drug groups experienced small increases (i.e., 1.8 mm Hg for venlafaxine and 0.6 mm Hg for imipramine) that were not statistically significant.

Effects of Venlafaxine Dosage on Blood Pressure

There was a strong relationship between venlafaxine dosage and change in blood pressure during acute phase therapy (dosage effect: F = 6.64, df = 3, 2801; p < .001). The dosage × time interaction term was not statistically significant (F = 1.38, df = 18, 104; p = .124).

Figure 3. Cumulative Percentage of Patients Developing Sustained Blood Pressure Elevation During Acute Phase Therapy



The crude rates of sustained elevation of SDBP across dosage groups were as follows: placebo, 2.2% (13/592); ≤ 100 mg/day venlafaxine, 1.7% (15/883); 101–200 mg/day venlafaxine, 3.5% (42/1201); 201–300 mg/day venlafaxine, 3.7% (17/462); and > 300 mg/day venlafaxine, 9.1% (17/186) ($\chi^2 = 31.7$, df = 4, $p < .001$). This relationship was not affected by controlling for age and sex effects in the survival analysis (log rank $\chi^2 = 25.7$, df = 3, $p < .001$) (Figure 3).

DISCUSSION

These results further clarify the effects of venlafaxine on blood pressure. In dosages of 300 mg/day or less, venlafaxine therapy did not significantly increase rates of sustained SDBP elevation when compared with placebo (i.e., 2.9% versus 2.2%). Importantly, venlafaxine therapy actually had a modestly beneficial impact on blood pressure among the patients with high pretreatment SDBP values. Venlafaxine therapy also had only a small effect on the SDBPs of patients with treated hypertension.

The effects of venlafaxine on blood pressure were strongly dose dependent. Of note, the incidence of elevated SDBP was 3 times greater among patients treated with more than 300 mg/day than among those treated with lower doses during acute phase therapy (i.e., 9% vs. 3%). Across doses, venlafaxine was associated with a small but statistically significant increase in incidence of subsyndromal blood pressure elevations, a greater persistence of effect during continuation therapy, and a small but significant incidence of new cases of elevated SDBP during longer term therapy.

Results of this study also illustrate that elevated SDBP can be observed during treatment with placebo and other types of antidepressants. A risk of increased blood pressure is reported in the *Physicians' Desk Reference* for virtually all of the tricyclics, although incidence rates are not listed. In this study, the rate of JNC V–defined elevated SDBP during imipramine therapy (4.7%) was virtually identical to the rate observed across all doses of venlafaxine (4.8%).

Is the rate of elevated SDBP observed during imipramine therapy in this study spuriously high? To my knowledge, this is the largest series of imipramine-treated cases with serial blood pressure monitoring ever described. Generally, the larger the sample size, the more reliable the finding. Perhaps the most rigorous study of imipramine effects on blood pressure was conducted by Glassman et al.[24] nearly 20 years ago. They reported that imipramine treatment (3.5 mg/kg) had no effect on supine systolic blood pressure during a careful, prospective 6-week study of 44 patients (intent-to-treat N = 50). However, their sample was older (mean = 59 years), and about 40% of the patients had significant cardiovascular disease. Beyond these methodological and sample differences, it is also possible that a problem with a 5% incidence could go

unnoticed in a study of 44 patients (i.e., only 2 treatment-emergent cases would have been observed by chance). A true mean increase of only 1 mm Hg (SD = 8.2) during imipramine therapy, as observed in this report, would necessitate a study group of over 300 people in order to have adequate statistical power.

Several trends suggested that the increases in blood pressure during imipramine therapy observed in this study were relatively benign. For example, no imipramine-treated patient had an increase in SDBP of ≥ 20 mm Hg, and none were withdrawn from the trial because of elevated SDBP. There were also fewer cases of "subthreshold" blood pressure elevation during acute phase therapy (vis-à-vis venlafaxine). Finally, three fourths of the cases with elevated SDBP remitted spontaneously during continuation pharmacotherapy with imipramine.

Although the findings of the current study could be anomalous, it is more likely that a problem with a relatively low incidence has been overlooked in smaller studies or obscured in larger studies that utilized less standardized assessment of blood pressure. The most rigorous studies of effects of tricyclics on blood pressure have focused on older patients, often with serious cardiovascular disease, and such patients may be more prone to develop orthostatic hypotension than elevated SDBP.[25] In clinical terms, the risk of orthostatic hypotension during tricyclic pharmacotherapy is far more important than elevations of blood pressure.

Several other classes of antidepressants also have significant effects on blood pressure. The nonselective monoamine oxidase inhibitors (MAOIs), for example, cause relatively high rates of orthostatic hypotension, in addition to their more notorious risk for hypertensive crises.[26] The aminoketone compound bupropion has been shown to increase SDBP,[27] although neither dose-response relationships nor the exact incidence of sustained SDBP elevation has been examined in detail. However, like venlafaxine, bupropion has a low risk of orthostasis and few anticholinergic or antihistaminergic side effects.[27]

The common link among the antidepressants that increase blood pressure may be potentiation of noradrenergic neurotransmission. In the paroxysmal hypertensive crises associated with MAOI therapy, high levels of unmetabolized tyramine or sympathomimetics trigger norepinephrine release from peripheral sympathetic neurons.[26] For other antidepressants, norepinephrine reuptake inhibition is most likely the cause of the less dramatic, nonemergent blood pressure elevations. Preclinical studies[1] suggest that the dose-dependent effect of venlafaxine on blood pressure might even serve as a "biological" assay of in vivo noradrenergic effects.

In 1998, the clinical relevance of increased blood pressure during venlafaxine therapy must be placed within the context of the SSRIs.[28] It is not clear if the SSRIs have any appreciable effect on blood pressure. Two published double-blind studies have contrasted the effects of venlafaxine and fluoxetine directly, and no significant differences in blood pressure were observed.[29,30] However, these studies were too small to be able to reliably detect small (e.g., 2% to 3%) differences in the incidence of elevated blood pressure. Moreover, only one of these studies permitted venlafaxine doses above 150 mg/day. Large databases exist for each of the SSRIs, and it would be beneficial to the field if proprietary boundaries were relaxed so that more definitive comparisons can be performed.

There are several limitations to this meta-analysis that deserve comment. First, despite the large overall sample size, the number of cases treated with placebo or imipramine in the longitudinal data set is quite small. Second, all of the patients were enrolled in controlled clinical trials and thus may not be fully representative of the general population of patients treated with antidepressants. For example, study patients were screened with a comprehensive medical examination, and those with serious comorbidities were excluded from research participation. The higher incidence of elevated SDBP observed in males and older patients, irrespective of treatment type, would suggest that some people are more vulnerable than others to develop increases in blood pressure during antidepressant therapy.

In addition, patients with severe cardiac conduction defects or poorly compensated congestive heart failure were excluded from the study. Although available evidence suggests that venlafaxine is less cardiotoxic than imipramine in overdose,[2,31,32] it is also true that its effects on cardiovascular function are not yet as well documented as those of the SSRIs. Of note, Roose et al.[9] found fluoxetine to be well tolerated but relatively ineffective compared with nortriptyline in a retrospective study of severely depressed elderly patients with significant heart disease. A prospective study comparing venlafaxine, nortriptyline, and an SSRI in depressed inpatients with heart disease would provide very useful information on relative tolerability and efficacy.

A final point of discussion concerns the statistical methods employed. Unlike conventional meta-analyses, which rely on summary statistics of grouped data, a meta-analysis of original data utilizes all data points for all subjects. This particular data set included more than 20,000 blood pressure measurements, providing a profound level of statistical power. A meta-analysis of original data also permits the effects of time, relevant covariates, drug type, and the interactions of these variables to be examined. Of course, artifacts can be introduced if the studies vary systematically in subject characteristics or methods. However, standardization of assessments and treatment protocols across studies, as was the case here, decreases the likelihood of such artifacts.[33]

Several options exist for management of a treatment-emergent increase in blood pressure during antidepressant

therapy. These options include continued observation, dosage reduction, discontinuation of the medication, treatment with an alternate antidepressant, or concomitant therapy with an antihypertensive. Clinical judgment should be used to select among these options, guided by the magnitude of the blood pressure elevation and the patient's response to treatment, history of nonresponse to other medications, and general medical status. As even the depressed patients treated with placebo in this study had a 2.2% risk of developing elevated blood pressure, physicians treating depressed patients with any type of antidepressant should be prepared to monitor blood pressure periodically.

In summary, a meta-analysis of original data found that treatment with venlafaxine at doses of 300 mg/day or less was not associated with a statistically or clinically significant risk of a sustained elevation of SDBP. Moreover, venlafaxine did not have deleterious effects on the control of blood pressure for patients with preexisting hypertension or elevated pretreatment SDBP. Concerns about the effects of venlafaxine on blood pressure, therefore, should not justify excluding it from first-line use. However, 2% to 4% of the patients treated with placebo, imipramine, or venlafaxine experienced a sustained elevation of SDBP, underscoring the potential importance for the psychiatrist to monitor patients' general medical status. The risk of a sustained increase in SDBP during high-dose (> 300 mg/day) venlafaxine treatment was found to be both statistically and clinically significant. It appears that this risk can be lessened by ensuring that a patient receives an adequate trial at moderate dosages (i.e., 150–250 mg/day) before advancing to higher dosages of venlafaxine. For those patients who require doses above 300 mg/day, careful serial monitoring of blood pressure is clearly indicated.

Drug names: bupropion (Wellbutrin), fluoxetine (Prozac), imipramine (Tofranil and others), venlafaxine (Effexor).

REFERENCES

1. Holliday SM, Benfield P. Venlafaxine: a review of its pharmacology and therapeutic potential in depression. Drugs 1995;49:280–294
2. Feighner JP. Cardiovascular safety in depressed patients: focus on venlafaxine. J Clin Psychiatry 1995;56:574–579
3. Thase ME, for the Venlafaxine XR 209 Study Group. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. J Clin Psychiatry 1997;58:393–398
4. Cunningham LA, for the Venlafaxine XR 208 Study Group. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Ann Clin Psychiatry 1997;9(3): 157–164
5. Thase ME, Howland RH. Biological processes in depression: an updated review and integration. In: Beckman EE, Leber WR, eds. Handbook of Depression. 2nd ed. New York, NY: Guilford; 1995:213–279
6. Delgado PL, Price LH, Heninger GR, et al. Neurochemistry. In: Paykel ES, ed. Handbook of Affective Disorders. 2nd ed. New York, NY: Guilford; 1992:219–253
7. Nelson JC. Are the SSRIs really better tolerated than the TCAs for treatment of major depression? Psychiatr Ann 1994;24:628–631
8. Potter WZ, Rudorfer MV, Manji H. The pharmacologic treatment of depression. N Engl J Med 1991;325:633–642
9. Roose SP, Glassman AH, Attia E, et al. Comparative efficacy of selective serotonin reuptake inhibitors and tricyclics in the treatment of melancholia. Am J Psychiatry 1994;151:1735–1739
10. Danish University Antidepressant Group. Citalopram: clinical effect profile in comparison with clomipramine: a controlled multicenter study. Psychopharmacology (Berl) 1986;90:131–138
11. Danish University Antidepressant Group. Paroxetine: a selective serotonin reuptake inhibitor showing better tolerance, but weaker antidepressant effect than clomipramine in a controlled multicenter study. J Affect Disord 1990;18:289–299
12. Pande AC, Sayler ME. Severity of depression and response to fluoxetine. Int Clin Psychopharmacol 1993;8:243–245
13. Fabre LF, Putman HP III. An ascending single-dose tolerance study of WY-45,030, a bicyclic antidepressant, in healthy men. Curr Ther Res 1987;42:901–909
14. Goldberg HL, Finnerty R. An open-label, variable-dose study of WY-45,030 (venlafaxine) in depressed outpatients. Psychopharmacol Bull 1988;24:198–199
15. American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, Third Edition, Revised. Washington, DC: American Psychiatric Association; 1987
16. Hamilton M. A rating scale for depression. J Neurol Neurosurg Psychiatry 1960;23:56–62
17. Reeves RA. Does this patient have hypertension? how to measure blood pressure. JAMA 1995;273:1211–1218
18. White WB, Lund-Johansen P, Omvik P. Assessment of four ambulatory blood pressure monitors and measurements by clinicians versus intraarterial blood pressure at rest and during exercise. Am J Cardiol 1990;65: 60–66
19. Robertson JIS. Guidelines for the treatment of hypertension: a critical review. Cardiovasc Drugs Ther 1994;8:665–672
20. Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure. The fifth report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure (JNC V). Arch Intern Med 1993;153:154–183
21. Lavori PW. Clinical trials in psychiatry: should protocol deviation censor patient data? reply to comments. Neuropsychopharmacology 1992;6: 61–63
22. Gibbons RD, Hedeker D. Application of random effects probit regression models. J Consult Clin Psychol 1994;62:285–296
23. Cox DR, Oakes D. Analysis of Survival Data. New York, NY: Chapman & Hall; 1984
24. Glassman AH, Bigger JTJ, Giardina EV, et al. Clinical characteristics of imipramine-induced orthostatic hypotension. Lancet 1979;1:468–472
25. Glassman AH, Roose SP, Giardina E-GV, et al. Cardiovascular effects of tricyclic antidepressants. In: Meltzer HY, ed. Psychopharmacology: The Third Generation of Progress. New York, NY: Raven Press; 1987: 1437–1442
26. Thase ME, Trivedi MH, Rush AJ. MAOIs in the contemporary treatment of depression. Neuropsychopharmacology 1995;12:185–219
27. Roose SP, Dalack GW, Glassman AH, et al. Cardiovascular effects of bupropion in depressed patients with heart disease. Am J Psychiatry 1991; 148:512–516
28. Thase ME. Antidepressant options: venlafaxine in perspective. J Clin Psychopharmacol 1996;16(suppl 2):10S–20S
29. Clerc GE, Ruimy P, Verdeau-Paillés J, on behalf of the Venlafaxine French Inpatient Study Group. A double-blind comparison of venlafaxine and fluoxetine in patients hospitalized for major depression and melancholia. Int Clin Psychopharmacol 1994;9:139–143
30. 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
31. Kapur S, Mieczkowski T, Mann JJ. Antidepressant medications and the relative risk of suicide attempt and suicide. JAMA 1992;268:3441–3445
32. Henry JA, Alexander CA, Sener EK. Relative mortality from overdose of antidepressants. BMJ 1995;310:221–223
33. Thase ME, Greenhouse JB, Frank E, et al. Treatment of major depression with psychotherapy or psychotherapy-pharmacotherapy combinations. Arch Gen Psychiatry 1997;54:1009–1015