ORIGINAL ARTICLE

Evidence of the Dual Mechanisms of Action of Venlafaxine

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Background: Indirect evidence suggests that the antidepressant venlafaxine hydrochloride selectively inhibits its serotonin (5-HT) uptake at low doses, whereas at high doses, it inhibits both 5-HT and norepinephrine (NE) uptake. We hypothesized that, in vivo, both high and low doses would inhibit the 5-HT uptake of platelets but that the higher dose would differentially blunt the pressor response to tyramine, a marker for NE uptake.

Methods: Healthy male volunteers aged 18 to 45 years received either 75 mg or 375 mg of venlafaxine hydrochloride per day, the 5-HT uptake inhibitor sertraline hydrochloride (50 mg/d), or the NE uptake inhibitor maprotiline hydrochloride (150 mg/d) (n = 8 for each of 4 treatment groups). Changes in platelet 5-HT uptake and the pressor response to intravenous tyramine were assessed following the initial dose and after 1 and 2 weeks of drug administration.

Results: Platelet 5-HT uptake was inhibited by venlafaxine across the dose range and by sertraline but not maprotiline. Inhibition was competitive, related to increases in affinity and not related to capacity. Steady-state drug levels were associated with a 5-HT uptake inhibition of 87% or more in subjects taking venlafaxine or sertraline. The pressor response to tyramine differentially distinguished maprotiline from sertraline and the low dose of venlafaxine but not from the high dose of venlafaxine.

Conclusion: This study provides the first in vivo evidence in healthy humans that both 5-HT uptake and NE uptake inhibition are mechanisms of action sequentially engaged by venlafaxine over its clinically relevant dose range.

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VENLAFAXINE hydrochloride[1] is an antidepressant with a mechanism of action that is believed to involve inhibition of the uptake pumps for serotonin (5-HT) and norepinephrine (NE)[2] with inhibition of NE uptake particularly relevant at higher doses. Preclinically, noradrenergic neurons had a biphasic dose-dependent response to venlafaxine,[2] and high doses caused rapid desensitization of β-adrenergic receptors,[3] reminiscent of that achieved when a selective serotonin reuptake inhibitor (SSRI) is combined with desipramine hydrochloride.[4] Clinically, venlafaxine hydrochloride, 375 mg/d led to a more rapid onset of antidepressant efficacy than did 75 mg/d.[5] Furthermore, venlafaxine has an ascending dose–antidepressant response curve[6] inconsistent with a single, saturable mechanism of action. Finally, the adverse effect profile of venlafaxine hydrochloride at 75 mg/d is typical of an SSRI (nausea, vomiting, gastrointestinal disturbances, and sexual dysfunction), but at higher doses, patients also experience effects similar to those of an NE uptake inhibitor (increased sweating, dry mouth, increased heart rate, and increased blood pressure). Although this pharmacological profile is consistent with the putative dual mechanisms of action of venlafaxine, this characteristic has not been directly examined in humans. Evidence that both mechanisms contribute to the action of venlafaxine would support short-term 5-HT and NE potentiation as separate routes to antidepressant efficacy.

This study tested 2 hypotheses: (1) Treatment with either a low (75 mg/d) or high (375 mg/d) dose of venlafaxine hydrochloride would inhibit 5-HT uptake. (2) Treatment with the high dose would cause a blunting of the pressor response to tyramine not apparent during treatment with the low dose. The uptake of 5-HT into platelets is used to model the function of the central 5-HT reuptake pump, illustrated in **Figure 1** (top).[7,8] Using this model, SSRIs demonstrate uptake inhibition in excess of 60% at their usually effective minimum doses.[9-15] The pressor response to an intravenous (IV) injection of tyramine is used to assess the function of the NE uptake pump.[7] As illustrated in Figure 1 (bottom), tyramine is taken into the nerve terminal by the NE

SUBJECTS, MATERIALS, AND METHODS

SUBJECTS

Male volunteers aged 18 to 45 years were recruited from the community via advertisements for healthy subjects to participate in a research study. All subjects were normotensive, nontobacco users, with body weight within 30% of the reference range as determined by actuarial tables. To minimize variability in venlafaxine plasma levels, subject's phenotypes were categorized as rapid metabolizers via cytochrome P450 2D6 using a dextromethorphan challenge test. Subjects were excluded if there was any clinically notable abnormality on findings from prestudy physical examination, laboratory tests, or electrocardiogram; a history or presence of a clinically notable disease; any psychiatric disorder; use of any prescription medication within 4 weeks or any nonprescription medication within 2 weeks prior to study drug administration; or systolic or diastolic blood pressure was greater than or equal to 135 mm Hg or 95 mm Hg, respectively. The study was approved by the Via Christi Institutional Review Board, Wichita, Kan. All volunteers provided written, informed consent, and subjects were paid for their participation.

PROCEDURES

On the evening of day −2, subjects were admitted to the Center for Phase I Research, a residential research unit affiliated with Via Christi Health System. They remained there for the duration of the study, maintained on a tyramine- and dopamine-controlled diet recommended by a hospital dietitian. Subjects were assigned randomly and in equal numbers (n = 8) (with replacement of noncompleters) to each of 4 treatment groups: low-dose venlafaxine hydrochloride (75 mg/d), high-dose venlafaxine hydrochloride (375 mg/d), sertraline hydrochloride (50 mg/d), or maprotiline hydrochloride (150 mg/d). Subjects receiving venlafaxine hydrochloride received a single 37.5-mg dose on day 1 and 75 mg/d beginning on day 2. Those assigned to the high-dose venlafaxine group were further advanced in 75-mg increments to a final dose of 375 mg/d on day 8. Subjects receiving maprotiline were titrated from 75 mg/d on day 1 to 150 mg/d on day 8.

Assessments were made at 5 time points: (1) 1 day prior to drug initiation (day −1); on the first day of treatment both (2) before (day 1, AM) and (3) after (day 1, PM) the initial dose; and after (4) 1 week (day 8) and (5) 2 weeks (day 15) of treatment. Blood for analysis of platelet 5-HT uptake and plasma drug levels was drawn between 7 AM and 8:30 AM on each assessment day. The day 1 PM sample was obtained between 5:30 PM and 6:30 PM. Administration of the initial dose was timed such that obtaining the blood sample occurred at approximately the time of peak plasma drug concentrations—1.5 hours postdose for venlafaxine,[16] 5.5 hours postdose for sertraline,[17] and 11.5 hours postdose for maprotiline.[18] A pressor test followed each blood sample except on day 1 when only the day 1 PM pressor test was conducted.

Levels of the parent compounds and the metabolites O-desmethylvenlafaxine and desmethylsertraline were determined. In the case of venlafaxine, the parent compound and equipotent[19] metabolite were combined to describe antidepressant drug levels.

PLATELET 5-HT UPTAKE

Analysis followed the general methods of Tuomisto.[20] Blood, collected into tubes containing potassium EDTA, was centrifuged (130*g* × 20 minutes) to yield platelet-rich plasma. Total uptake was determined by adding the platelet-rich plasma (100 µL) to ^{3}H-5-HT (final concentration, 0.1 µmol-1.0 µmol) in Krebs-Henseliet bicarbonate buffer (3.9 mL),

uptake pump, it displaces NE from intracellular stores leading to NE release, and the NE produces a transient increase in blood pressure. Blockade of the uptake pump causes the pressor effect to be blunted in proportion to the extent of uptake pump inhibition. In this study, sertraline hydrochloride and maprotiline hydrochloride served as positive and negative controls for the effects on 5-HT and NE uptake, respectively.

RESULTS

Thirty-four subjects were enrolled. One subject withdrew consent prior to drug administration, and one discontinued halfway through treatment owing to a death in the family. The treatment groups did not differ based on age, weight, or ethnicity (**Table 1**). Adverse effects were all of mild severity and were reported by 2 subjects in each venlafaxine group, 1 in the sertraline group, and 4 in the maprotiline group. No subject experienced any unexpected increase in blood pressure that required intervention. Levels of each antidepressant and measured metabolites are given in **Table 2**.

PLATELET 5-HT UPTAKE

Platelet 5-HT uptake was inhibited during treatment with venlafaxine or sertraline but not with maprotiline. Affinity increased with both the low dose ($\chi^2_4 = 11.87$, $P = .02$) and the high dose ($\chi^2_4 = 16.16$, $P = .003$) of venlafaxine (**Table 3**). Inhibition became increasingly apparent during the course of the 2-week treatment. The 95% confidence intervals (CIs) surrounding average baseline values in the low-dose venlafaxine group (critical difference for 2 comparisons, 1.75) included day 8 (test statistic, 1.63) and was just reached at day 15 (test statistic, 1.75). In the high-dose venlafaxine group, 95% CIs were exceeded on both day 8 (test statistic, 2.25) and day 15 (test statistic, 2.13). Sertraline caused the expected increase in K_m ($\chi^2_4 = 22.60$, $P<.001$), and values exceeded 95% CIs at day 8 (test statistic, 2.88) and day 15 (test statistic, 2.25). When day 1 PM comparisons were included (critical difference for 3 comparisons, 1.86), neither the low-dose (test statistic, 0.69) or high-dose (test statistic, 0.63) venlafaxine groups nor the sertraline (test statistic, 1.75) group lay outside the 95% CIs. Affinity

incubating the mixture at 37°C for 5 minutes. After terminating uptake by rapid cooling to 4°C and filtration, radioactivity accumulated to the filter was measured. Nonspecific uptake was determined simultaneously in an ice bath.

Active uptake was calculated as the difference between total and nonspecific uptake at each 5-HT concentration. Affinity (K_m) and capacity (V_{max}) of active uptake were determined using a Lineweaver-Burk plot. Uptake inhibition (as measured in the assay) was related to plasma drug concentration (as measured in subjects in the venlafaxine group) as follows. Mean 5-HT uptake inhibition at the 3 intermediate 5-HT concentrations was determined at each posttreatment time point. All posttreatment time points for all subjects in the venlafaxine groups were used to mathematically derive the inhibition constant, K_i, which was then used to extrapolate assay results (obtained after dilution of the plasma) to the original plasma levels of the study subjects.

PRESSOR RESPONSE TO TYRAMINE

Tyramine was obtained from Research Biochemicals International (RBI, Natick, Mass) and prepared as 2-mg/mL saline with ascorbate. The pyrogenicity and sterility of each batch of prepared drug were assessed prior to use. During the pressor test, phentolamine mesylate (5 mg) was always available to be injected IV in the event of a hypertensive crisis.

The assay followed the general methods of Ghose et al.[7,21] An IV catheter was inserted, and continuous electrocardiogram monitoring was begun. Resting blood pressure levels were obtained every 5 minutes for 30 minutes; the average of these measurements formed the baseline values. Successive increasing doses of tyramine were then injected. After each injection, blood pressure levels were allowed to return to baseline before advancing to the next dose. Once an injection was complete, blood pressure levels were recorded every 30 seconds for the first 3 minutes, and then at 4, 5, 7, and 9 minutes.

After an initial dose of 0.25 mg of tyramine to test for sensitivity, additional doses began at 3 mg and were increased in 3-mg increments. During the initial (day –1) pressor test, dose escalation continued until an increase in blood pressure of at least 30 mm Hg over baseline systolic blood pressure was achieved. During subsequent pressor tests, dose escalation was further limited to the highest dose given during the day –1 test.

For each subject at each time point following antidepressant treatment, relative pressor response was expressed as the ratio of the maximum tyramine-induced increase in systolic blood pressure to the maximum increase on day –1. Comparisons were made at the highest tyramine dose common to both time points, one of which always achieved at least a 30–mm Hg increase in systolic blood pressure.

STATISTICAL ANALYSIS

To assess the effects of each treatment on K_m and V_{max}, planned comparisons of these parameters were made following Friedman 2-way analysis of variance by ranks within each drug group. The 3 postdrug time points were compared in reverse chronological order with the averaged predrug time points, and critical differences were adjusted as the number of comparisons increased. A statistically significant day 15 vs predrug comparison triggered an additional comparison at day 8. Statistical tests were not used to assess in vivo uptake inhibition because the dilution step of the assay required use of extrapolated values.

To assess the effects of each treatment on the pressor response, comparisons of all drug groups followed Kruskal-Wallis (KW) analysis of variance of day 15 data. All tests were 2-tailed, and a level of .05 was considered statistically significant throughout.

(K_m) did not change for the maprotiline group ($\chi^2_4 = 4.85$, $P = .30$). No changes in V_{max} were apparent in any treatment group ($\chi^2_4 < 7.31$, $P > .12$).

Assay data from all subjects taking venlafaxine were used to calculate a K_i of 15.9 ng (venlafaxine + O-desmethylvenlafaxine)/mL, or 52 nm. At the steady-state levels attained by subjects in the low-dose venlafaxine group, this K_i indicates 87% inhibition of platelet 5-HT uptake; in the high-dose group, inhibition reached 97%. The extent of in vivo inhibition was also examined more directly, circumventing the 40:1 dilution and subsequent extrapolation. Active uptake apparent after dilution of platelets was virtually abolished when the diluting buffer included either sertraline or venlafaxine in the concentrations developed by the volunteers. Uptake was also assessed in patients taking sertraline or venlafaxine. A replacement of just 25% of the diluent buffer with the patient's own platelet-poor but drug-rich plasma reduced platelet 5-HT uptake by 67%. Finally, the extrapolated conclusions are consistent with predictions derived from published values of K_i (**Table 4**), confirming the validity of the extrapolated data.

PRESSOR RESPONSE TO TYRAMINE

The 4 treatment groups did not differ in pretreatment autonomic function (**Table 5**). Following the initial dose, 1 of 2 venlafaxine groups demonstrated a significantly higher baseline systolic blood pressure than did the sertraline group. No other differences in baseline blood pressure were observed throughout the course of the study.

In most cases (Table 5) the tyramine dose pretreatment was required to determine relative pressor response posttreatment. Exceptions occurred when a 30–mm Hg increase in systolic blood pressure posttreatment was reached at a lower tyramine dose.

Overall, treatment group had a significant effect on pressor response at day 15 (KW[3] = 17.13, $P < .001$) (**Figure 2**). Posthoc comparisons of all groups distinguished both the low-dose venlafaxine and sertraline groups but not the high-dose venlafaxine from the maprotiline group (mean differences, 16.50, 16.75, and 8.75, respectively, vs a critical difference of 12.37). As predicted, the pressor response on day 15 was blunted more in subjects in the high-dose venlafaxine group than those

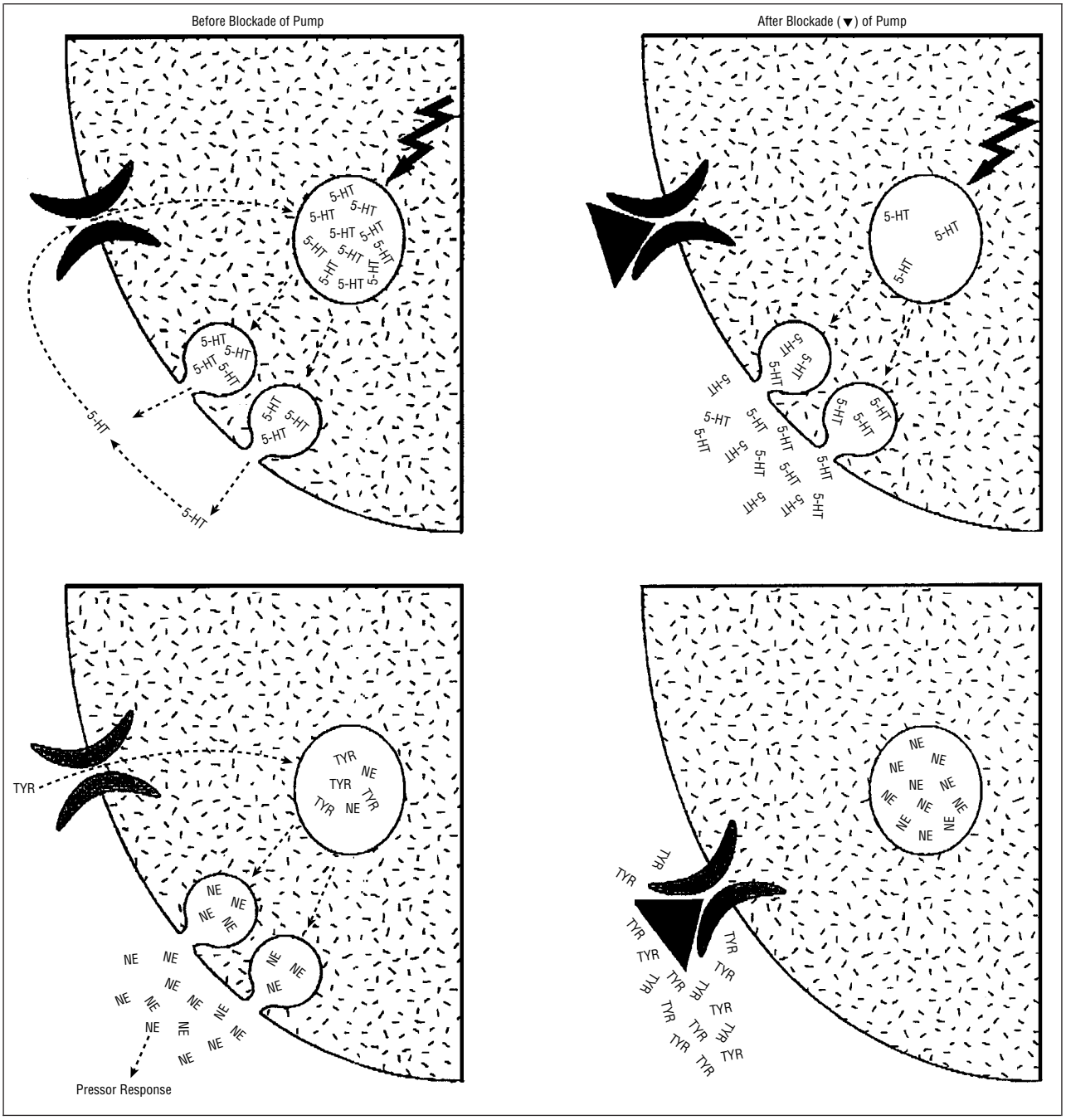

Figure 1. *Neurotransmitter uptake and models of serotonergic (top) and noradrenergic neurons (bottom). Top, Serotonin (5-HT) is released by the neuron. Its action is terminated by active reuptake into the neuron, where it is further sequestered in storage vesicles. Drugs that inhibit the 5-HT uptake pump reduce the accumulation of intracellular 5-HT and prolong extracellular action. Bottom, Tyramine (TYR) is taken into the norepinephrine (NE) neuron via the NE uptake pump. Inside the neuron, TYR displaces NE from storage vesicles. Norepinephrine is released from the cell and acts at the receptor sites of effector cells to elevate blood pressure. Drugs that inhibit the NE uptake pump prevent accumulation of TYR, subsequent displacement of NE, and blunt the pressor response.*

in the low-dose group (mean difference, 7.75 vs a critical difference of 12.37), though this difference failed to reach statistical significance. Similar but less robust responses were noted on day 8.

COMMENT

This study tested the hypothesis that venlafaxine at low doses inhibits 5-HT uptake and at high doses inhibits both 5-HT and NE uptake. Across the dosing range, venlafaxine inhibited 5-HT uptake as did the 5-HT control, sertraline, but not the NE control, maprotiline. In contrast, the low-dose venlafaxine and sertraline groups (but not the high-dose venlafaxine group) differentiated themselves from the maprotiline group on the pressor response to tyramine. These results are consistent with the theory that venlafaxine sequentially engages the mechanisms of 5-HT and NE uptake inhibition over its clinically relevant dose range.

The dose at which venlafaxine begins to have in vivo effects on NE uptake is of interest. The results of the high-

dose venlafaxine group are most germane since this group was actually tested using 3 dosage conditions: (1) after a single dose of 37.5 mg on day 1, (2) following 225 mg/d for 3 days on day 8, and (3) following 375 mg/d for 7 days on day 15. The pressor response to IV tyramine was blunted after venlafaxine hydrochloride, 375 mg/d, on day 15 (Figure 2); however, a less robust divergence from the 75 mg/d group was apparent even on day 8 after venlafaxine hydrochloride, 225 mg/d, for 3 days.

An unexpected observation was that a somewhat augmented pressor response to IV tyramine administration developed in the sertraline and low-dose venlafaxine groups in contrast to blunting with the high-dose venlafaxine and maprotiline groups. It is conceivable that this trend represented sensitization occurring after repeated exposure to IV tyramine rather than a specific effect produced by 5-HT potentiation. This possibility cannot be ruled out because there was no parallel placebo control group. One observation suggesting that the effect could be mediated by a 5-HT mechanism is the slightly enhanced pressor response in the high-dose venlafaxine hydrochloride group after the single dose of 37.5 mg/d on day 1. If augmentation of the pressor effect attends 5-HT potentiation, it could explain why high-dose venlafaxine did not produce the same degree of blunting as did maprotiline on day 15. Consistent with this line of reasoning, the magnitude of the difference between the 2 venlafaxine groups on day 15 (ie, the effect attributable to inhibition of the NE uptake pump) is virtually the same as the difference produced by maprotiline from baseline. Further work is needed to determine whether and by what mechanism 5-HT uptake inhibition might enhance the pressor response to IV tyramine.

Two limitations need to be considered when assessing the results from this study. First, peripheral rather than central measures were used to assess drug levels and drug effect on 5-HT and NE function. This approach was used because the peripheral measures are less invasive and have been widely used as surrogates for central

Table 1. Subject Characteristics*

Characteristic	Study Group			
	Venlafaxine, 75 mg/d	Venlafaxine, 375 mg/d	Sertraline, 50 mg/d	Maprotiline, 150 mg/d
Age, y	32.2 (9.0)	29.1 (8.2)	27.7 (6.5)	28.1 (8.7)
Weight, kg	78.9 (10.5)	80.0 (14.2)	83.7 (13.7)	87.1 (9.9)
Ethnicity, No. of subjects				
White	4	6	5	6
Hispanic	2	1	2	1
African American	2	1	1	1

Values are given as mean ± SD except where indicated. For each group, n = 8. Venlafaxine given as venlafaxine hydrochloride; sertraline, sertraline hydrochloride; and maprotiline; maprotiline hydrochloride.

Table 2. Plasma Levels of Drugs and Active Metabolites*

Drug and Active Metabolite	Study Group			
	Venlafaxine, 75 mg/d	Venlafaxine, 375 mg/d†	Sertraline, 50 mg/d	Maprotiline, 150 mg/d†
Parent compound, ng/mL				
Day 1, PM	30 (17)	30 (20)	12 (8)	22 (5)
Day 8	23 (19)	45 (29)	16 (6)	59 (21)
Day 15	21 (19)	107 (57)	16 (6)	116 (41)
Metabolite, ng/mL				
Day 1, PM	41 (27)	60 (30)	3 (4)	. . .
Day 8	101 (19)	271 (68)	24 (7)	. . .
Day 15	84 (17)	421 (108)	30 (11)	. . .

Values are given as mean ± SD. Levels were obtained at estimated time of occurrence for maximum drug concentration (t_{max}) for day 1, PM, and represent trough levels on day 8 and day 15. For venlafaxine, metabolite values are those of o-desmethylvenlafaxine; for sertraline, metabolite values are those of desmethylsertraline. Ellipses indicate not obtained. For each group, n = 8.

†*Final dose reached on day 8.*

Table 3. Parameters of Platelet Serotonin Uptake*

Parameter	Study Group			
	Venlafaxine, 75 mg/d	Venlafaxine, 375 mg/d†	Sertraline, 50 mg/d	Maprotiline, 150 mg/d
Affinity (K_m), µmol				
Day –1	0.21 (0.11)	0.29 (0.12)	0.19 (0.06)	0.24 (0.08)
Day 1, AM	0.32 (0.25)	0.30 (0.10)	0.28 (0.10)	0.22 (0.07)
Day 1, PM	0.32 (0.16)	0.38 (0.17)	0.77 (0.46)	0.26 (0.07)
Day 8	0.42 (0.16)	0.73 (0.28)‡	1.00 (0.41)§	0.23 (0.04)
Day 15	0.62 (0.46)§	0.76 (0.40)‡	1.00 (0.87)‡	0.19 (0.10)
Capacity (V_{max}), pmol/5 min/ 2×10^7 platelets				
Day –1	40.4 (13.1)	54.6 (22.1)	41.4 (11.1)	37.9 (22.9)
Day 1, AM	49.2 (23.9)	55.4 (23.9)	38.8 (14.2)	41.7 (16.0)
Day 1, PM	39.2 (15.3)	47.4 (19.4)	37.0 (11.1)	48.7 (11.5)
Day 8	53.4 (14.6)	52.4 (21.8)	42.1 (11.2)	49.0 (12.0)
Day 15	66.2 (37.7)	43.3 (18.7)	41.4 (36.3)	43.0 (16.7)

Values are given as mean ± SD. For each group, n = 8. Venlafaxine given as venlafaxine hydrochloride; sertraline, sertraline hydrochloride; and maprotiline; maprotiline hydrochloride.

†*Final dose reached on day 8.*

‡P<.05 *vs predrug (day –1 and day 1, AM, combined).*

§P<.01 *vs predrug (day –1 and day 1, AM, combined).*

measures. Nevertheless, they do not actually measure the free concentration of the drug in the synapse or the degree of blockade of the central transporter. Second, it was necessary to estimate the degree of in vivo inhibition of 5-HT uptake inhibition by venlafaxine, taking into account the dilution step in the in vitro platelet 5-HT uptake assay. This dilution step is used to minimize changes in uptake rate and to ensure that uptake is measured during the initial linear stages as required for kinetic analyses.[20] This study and other recent literature[23] demonstrate that the K_m of the inhibitor for the uptake pump determines the magnitude of the dilution effect and must be taken into account when analyzing such data. Dilution effects apparent when working with low-affinity drugs can be minimized in future studies by using assays requiring little or no dilution of plasma.[7,24,25]

Table 4. Comparison of Observed vs Predicted Serotonin Uptake Inhibition by Venlafaxine*

Measure	Study Group: Venlafaxine, 75 mg/d	Study Group: Venlafaxine, 375 mg/d
Plasma levels of active components, ng/mL†	105.2	527.7
Plasma concentration of active components, nm	341.9	1715.0
Reported K_i, nm‡	39.0	39.0
Inhibition in vivo calculated from reported K_i, %§	89.8	97.8
Inhibition in vivo calculated from assay data, %	86.9	97.0

*Values are given as means. For each group, n = 8. Venlafaxine given as venlafaxine hydrochloride.

†Venlafaxine plasma levels are from day 15 and include metabolite.

‡K_i's based on literature values for venlafaxine[22] and o-desmethylvenlafaxine.[19]

§Predicted percent inhibition calculated as % inhibition = 100 × [drug/(K_i + drug)].

This study provides additional evidence that there are mechanistically different antidepressants. Sertraline and other SSRIs seem to directly affect only 5-HT. Maprotiline and other NE selective reuptake inhibitors (eg, desipramine) seem to directly affect only NE. Based on the results of this study, venlafaxine seems to sequentially affect 5-HT and NE. This provides the clinician with a basis for understanding several aspects of the dose-response curves of the SSRIs and venlafaxine, including (1) the difference in dose–antidepressant response curves. Based on fixed-dose studies, the SSRIs as a class have flat dose–antidepressant response curves such that patients at each dose have approximately the same likelihood of responding. In contrast, the fixed-dose studies with venlafaxine found an ascending dose–antidepressant response curve. Our study suggests that increased efficacy with the increased dose of venlafaxine is a consequence of the sequential engagement of 5-HT uptake inhibition at low doses and NE uptake inhibition at higher doses. (2) Another aspect is the difference in dose–adverse effect curves. Serotonin selective reuptake inhibitors have ascending curves regarding dropout rates owing to adverse effects; the adverse effects (eg, nausea and loose stools) are consistent with excessive 5-HT potentiation. Venlafaxine also has an ascending curve regarding dropouts, but higher doses produce adverse effects consistent with NE potentiation (eg, elevated blood pressure) as well as 5-HT-mediated adverse effects. (3) These

Table 5. Autonomic Characteristics Associated With the Tyramine Pressor Test*

Characteristic	Study Group: Venlafaxine, 75 mg/d	Study Group: Venlafaxine, 375 mg/d	Study Group: Sertraline, 50 mg/d	Study Group: Maprotiline, 150 mg/d
Day –1				
Baseline systolic BP, mm Hg	115.9 (4.3)	111.5 (6.8)	113.4 (8.5)	114.9 (3.8)
Baseline diastolic BP, mm Hg	80.5 (4.0)	75.3 (5.1)	76.8 (5.8)	78.0 (3.0)
Dose of tyramine used, mg	9.4 (1.9)	7.9 (1.6)	9.4 (3.0)	9.4 (1.9)
Day 1, PM				
Baseline systolic BP, mm Hg†	124.6 (6.4)†	122.0 (7.6)	114.8 (8.6)†	117.8 (5.4)
Baseline diastolic BP, mm Hg	82.8 (4.6)	78.9 (7.0)	76.3 (7.0)	77.1 (4.2)
Dose of tyramine used, mg	8.3 (2.1)	7.1 (1.6)	8.3 (2.1)	9.0 (1.6)
No. of subjects reaching target at tyramine dose lower than day –1	3	2	2	1
Day 8				
Baseline systolic BP, mm Hg	113.9 (4.7)	119.3 (8.8)	113.4 (7.4)	119.6 (5.3)
Baseline diastolic BP, mm Hg	79.1 (6.4)	82.6 (7.2)	75.3 (5.7)	77.8 (9.0)
Dose of tyramine used, mg	7.9 (1.6)	7.5 (1.6)	7.9 (2.2)	9.4 (1.9)
No. of subjects reaching target at tyramine dose lower than day –1	4	1	4	0
Day 15				
Baseline systolic BP, mm Hg	117.6 (6.5)	120.5 (10.7)	112.9 (9.6)	120.6 (4.0)
Baseline diastolic BP, mm Hg	80.6 (5.4)	81.3 (5.6)	75.4 (7.3)	76.9 (5.9)
Dose of tyramine used, mg	7.9 (1.6)	7.5 (1.6)	8.3 (2.7)	9.4 (1.9)
No. of subjects reaching target at tyramine dose lower than day –1	3	1	4	0

*Values are given as mean ± SD except where indicated. Baseline measures obtained prior to tyramine test at each time point. BP indicates blood pressure. For each group, n = 8. Venlafaxine given as venlafaxine hydrochloride; sertraline, sertraline hydrochloride; and maprotiline; maprotiline hydrochloride.

†Group difference ($\chi^2_3 = 8.15$, P = .043); low-dose venlafaxine and sertraline groups differ from each other, P<.05.

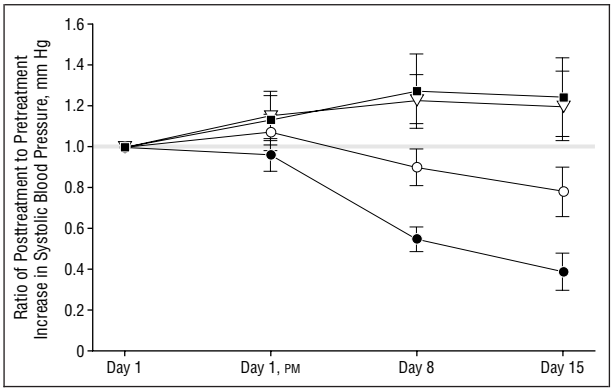

Figure 2. *Change in pressor response during the study for the 4 groups: (1) venlafaxine hydrochloride, 75 mg/d (open triangle), (2) venlafaxine hydrochloride, 375 mg/d of venlafaxine (open circle), (3) maprotiline hydrochloride, 150 mg/d (closed circle), or (4) sertraline hydrochloride, 50 mg/d (closed square). The maximum tyramine-induced increase in systolic blood pressure at each posttreatment time point was compared with the day 1 response at the highest tyramine dose common to both tests, with responses expressed as a multiple of the day 1 response. Mean and SE are shown. The sertraline and low-dose venlafaxine groups differed from the maprotiline group on days 8 and 15 (*$P<.05$*).*

results can explain why responders to low doses but not to high doses of venlafaxine experienced a transient recurrence of depressive symptoms when exposed experimentally to tryptophan depletion, which acutely but transiently depletes central 5-HT[26]: patients requiring higher doses of venlafaxine presumably had an antidepressant response, which was in whole or in part independent of 5-HT.

While the results of this study are heuristically useful as a means of understanding differences between mechanistically different classes of antidepressants, the study was not intended to compare relative clinical value. Future studies can be designed to directly compare venlafaxine with SSRIs and traditional 2-drug augmentation strategies[27] taking into account safety, tolerability, efficacy, cost-effectiveness, and ease of use in clinical practice.

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