Cytochrome P450 2D6 Phenotype Predicts Antidepressant Efficacy of Venlafaxine: A Secondary Analysis of 4 Studies in Major Depressive Disorder

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Introduction: Venlafaxine, a serotonin-norepinephrine reuptake inhibitor antidepressant, is metabolized primarily by the cytochrome P450 2D6 enzyme into O-desmethylvenlafaxine (ODV). The ODV/venlafaxine ratio can be used to distinguish between extensive metabolizers (EMs) and poor metabolizers (PMs).

Objectives: To determine the relative efficacy and tolerability of venlafaxine in EM vs PM patients with major depressive disorder (MDD).

Method: Data from 4 double-blind, placebo-controlled studies of patients with MDD were pooled. Blood samples were analyzed for plasma concentrations of venlafaxine, ODV, total venlafaxine + ODV, and ODV/venlafaxine ratio. Patients were classified as EMs or PMs on the basis of ODV/venlafaxine ratios. Changes from baseline in depression scale scores were compared between EMs and PMs using *t* tests. Rates of response, remission, discontinuation, and adverse events (AEs) were compared for EMs and PMs using Fisher exact tests.

Results: Compared with PMs, EMs had significantly greater mean changes from baseline on 4 of 5 depression rating scales (all 4 comparisons, $P \leq .020$). A significantly greater percentage of EMs achieved response or remission by most measures compared with PMs (4 of 5 comparisons, $P \leq .015$). Rates of discontinuation and AEs did not differ significantly between EMs and PMs. Since there were no substantial differences between EMs and PMs in terms of venlafaxine dose or tolerability, these factors are not likely to account for the efficacy findings.

Conclusions: Venlafaxine treatment in EMs was associated with greater efficacy in MDD on virtually all measures compared with PMs, with no important tolerability differences.

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The majority of antidepressants are metabolized by the hepatic cytochrome P450 (CYP) system.[1] One of the major enzymes in this system, CYP2D6, has a high degree of polymorphism, resulting in a variety of phenotypes among individuals, including poor metabolizers (PMs), intermediate metabolizers, extensive metabolizers (EMs), or ultrarapid metabolizers.[2] The majority of the human population can be classified as EMs, and approximately 5%–10% of Caucasians are classified as PMs.[1,3–7] The serotonin-norepinephrine reuptake inhibitor venlafaxine is principally metabolized by CYP2D6 to O-desmethylvenlafaxine (ODV).[8] Plasma concentrations of venlafaxine and ODV and the ratio of ODV to venlafaxine vary depending on the level of CYP2D6 activity. EMs have higher ODV/venlafaxine ratios compared with PMs,[8] and the ratio of ODV to venlafaxine concentrations can be used to distinguish EMs from PMs.[9–11] A recent analysis found that EMs had ODV/venlafaxine ratios consistently ≥ 1, whereas PMs had ratios < 1.[11]

Two small-scale studies have reported an association between the efficacy of venlafaxine in the treatment of major depressive disorder (MDD) and the CYP2D6 metabolizer phenotype, as determined by ODV/venlafaxine concentration ratios, with higher ratios associated with greater efficacy.[10,12] Other studies have found an association between genotype and tolerability of antidepressants metabolized by CYP2D6 (including venlafaxine); specifically, PMs were more likely to experience poor tolerability compared with EMs.[9,13–15] However, these studies were relatively small (ie, 22–136 subjects),[9,10,12–15] and most failed to demonstrate differences in antidepressant efficacy between EMs and PMs (genotype or phenotype).[9,13–15] The objective of this analysis was to determine in a large sample if there is an association between patients' CYP2D6 metabolizer status (EM or PM, as determined by the ODV/venlafaxine ratio) and the efficacy of venlafaxine in MDD; safety and tolerability were also evaluated.

METHOD

Study Design

Data from 4 short-term (6–12 weeks), randomized, double-blind, placebo-controlled studies (protocols 203, 208, 209, and 313)[16–19] were pooled for analysis. Two of the studies used fixed doses of venlafaxine immediate release (IR) (dose range: 75 mg/d to 375 mg/d); the other 2 used flexible dosing (venlafaxine extended release [ER], or IR, 75–150 mg/d; venlafaxine ER 25–225 mg/d). These studies represent all Wyeth-sponsored venlafaxine (IR or ER) double-blind, placebo-controlled clinical studies of adult outpatients with major depression (*DSM-III* or *DSM-III-R* criteria) or MDD (*DSM-IV* criteria) for which ODV and venlafaxine plasma concentration data were available.

Assessment and Classification of Metabolizer Status

Plasma concentrations. Plasma concentrations evaluated in the current analysis included ODV concentration,

venlafaxine concentration, total ODV + venlafaxine concentration, and the ODV/venlafaxine ratio. These values were determined from blood samples drawn at various time points, ranging from 10 minutes to 55 hours postdose on study days 14, 42, 56, and 84, or on the last day of full-dose treatment.

Cytochrome P450 2D6 EM and PM phenotypes were determined based on the ratio of ODV to venlafaxine concentrations. Prior studies have shown the ODV/venlafaxine ratio to be a valid indicator of CYP2D6 activity and also that it is correlated with CYP2D6 genotype.[9–11] When information was available, the classification rules took into account differences in sampling times; patients with ODV/venlafaxine ratios ≥ 1 were classified as EMs, and those with ratios < 1 were classified as PMs. These assignment criteria have previously been described.[11] This method of phenotype classification based on the ODV/venlafaxine ratio does not allow for the granular distinction among intermediate metabolizers, EMs, and ultrarapid metabolizers; these 3 groups are collapsed into 1 (EMs).

Concomitant CYP2D6 medications. Because chronic administration of CYP2D6 inhibitors can be a potential confounding factor by creating conversion to the PM phenotype ("phenocopy"), the use of concomitant nonstudy medications that were capable of inhibiting CYP2D6 during the study treatment periods was assessed.

Outcome Measures

Efficacy. The primary outcome measure in the individual studies was the 17-item Hamilton Depression Rating Scale ($HDRS_{17}$)[20]; other efficacy assessments included the $HDRS_6$ (Bech version),[21] the Montgomery-Asberg Depression Rating Scale (MADRS),[22] and the Clinical Global Impressions–Improvement (CGI-I) and Severity of Illness (CGI-S) scales.[23] Data were analyzed from the final on-therapy assessment, using the last observation carried forward to account for missing data. Changes from baseline and percentage improvement for all 4 measures were calculated.

Additional efficacy outcome measures, determined a priori, included response, defined as ≥ 50% reduction from baseline of the $HDRS_{17}$ or MADRS total scores, and remission, defined as $HDRS_{17}$ total scores ≤ 7 or MADRS total scores ≤ 12.

Safety and tolerability. Discontinuation rates, reasons for discontinuation, and treatment-emergent adverse events (TEAEs) were examined to evaluate safety and tolerability.

Statistical Analysis

Formulation. Two of the 4 studies used an IR formulation of venlafaxine, 1 study used an ER formulation, and 1 study included both ER and IR treatment arms. Therefore, to avoid any potential confounding factors resulting from formulation type, analyses were performed to examine whether there was an effect of formulation on efficacy. A 2-way analysis of variance was conducted, with formulation, phenotype, and the interaction between formulation and phenotype as independent variables and change from baseline on $HDRS_{17}$ total score as the dependent variable.

Dose and plasma concentrations. Summary statistics of dose and plasma concentrations for EMs and PMs were generated.

Concomitant CYP2D6 medications. The use of medications that inhibit CYP2D6 during the study treatment period was summarized and compared between patients in the venlafaxine (EM vs PM) and placebo groups using the Fisher exact test.

Efficacy. Changes from baseline for $HDRS_{17}$, $HDRS_6$, MADRS, and CGI-S scores and CGI-I scores at the final on-therapy assessment were summarized with mean and standard deviation for EM and PM patients, and *t* tests were used to compare the 2 groups. Rates of response and remission were summarized for EM and PM patients and compared between groups using the Fisher exact test. Efficacy outcomes for the placebo group were also determined and were compared with each of the metabolizer groups. The placebo-treated patients were not phenotyped and very likely included both EMs and PMs. Pearson correlations (*r*) were used to evaluate the relationship between various efficacy variables and ODV and venlafaxine plasma concentrations.

Safety. Reasons for discontinuation and TEAEs were summarized and compared between EMs, PMs, and placebo-treated patients using the Fisher exact test. There was no statistical correction for multiple comparisons.

RESULTS

Patients

The safety population included a total of 836 patients. Six patients randomly assigned to placebo had no efficacy data. Data from 830 patients were included in the efficacy analysis: 464 received venlafaxine, (415 [89%] and 49 [11%] of whom were EMs and PMs, respectively), and 366 received placebo. Demographic and baseline characteristics of EMs and PMs are presented in Table 1. Differences in the distribution of ethnic origin and sex between phenotypes were not significant. Baseline mean scores on the $HDRS_{17}$, $HDRS_6$, MADRS, and CGI-S also were comparable between EMs, PMs, and placebo-treated patients.

Formulation

There was no interaction between formulation (IR vs ER) and phenotype (EM vs PM) on efficacy (measured as change from baseline in $HDRS_{17}$ total score) and no significant main effect of formulation on efficacy. Therefore, the remaining analyses on efficacy were conducted using pooled data from studies using both formulations.

Concomitant CYP2D6 Medications

There were no significant overall or pairwise differences between groups for total percentage of CYP2D6 inhibitor use (7% EMs, 8% PMs, and 10% placebo). The most frequently used CYP2D6 inhibitors included H_2-receptor antagonists (3%) and sympathomimetics (2%), which are weak CYP 2D6 inhibitors.[24]

Table 1. Baseline Demographic and Clinical Characteristics of 836 Patients With Major Depressive Disorder Treated With Venlafaxine or Placebo by Metabolizer Status

Characteristic	Venlafaxine EM, n = 415	Venlafaxine PM, n = 49	Placebo, n = 372	*P* Value
Age, y				.697[a]
Mean (SD)	40.62 (10.64)	41.80 (10.70)	40.40 (11.16)	
Range	18–72	19–66	18–77	
Median	40	41	39	
Sex, n (%)				.073[b]
Female	250 (60)	34 (69)	203 (55)	
Male	165 (40)	15 (31)	169 (45)	
Ethnic origin, n (%)				.230[b]
Black	27 (7)	2 (4)	18 (5)	
Hispanic	14 (3)	1 (2)	4 (1)	
Other	7 (2)	0	11 (3)	
White	367 (88)	46 (94)	339 (91)	
$HDRS_{17}$ total score				.433[a]
n	415	49	366	
Mean (SD)	22.32 (3.21)	22.82 (3.32)	22.20 (3.12)	
$HDRS_6$ total score				.182[a]
n	415	49	366	
Mean (SD)	12.60 (1.76)	12.61 (1.72)	12.38 (1.58)	
MADRS total score				.778[a]
n	414	49	362	
Mean (SD)	28.14 (5.85)	28.57 (5.93)	27.99 (5.21)	
CGI-S score				.663[a]
n	413	49	361	
Mean (SD)	4.30 (0.59)	4.22 (0.65)	4.30 (0.56)	

[a]One-way analysis of variance with treatment sequence as factor.
[b]Fisher exact test *P* value (2-tailed).
Abbreviations: CGI-S = Clinical Global Impressions–Severity of Illness scale, EM = extensive metabolizer, $HDRS_6$ = 6-item Hamilton Depression Rating Scale, $HDRS_{17}$ = 17-item Hamilton Depression Rating Scale, MADRS = Montgomery-Åsberg Depression Rating Scale, PM = poor metabolizer.

Table 2. Dose and Plasma Concentrations in 464 Patients With Major Depressive Disorder Treated With Venlafaxine, by Metabolizer Status

Variable	*P* Value (*t* test)	EM, n = 415	PM, n = 49
Dose, mg	.963		
Mean (SD)		129.08 (68.30)	128.60 (60.47)
Median		129.75	132.69
Range		19.74–339.62	22.97–316.35
Plasma sample taken, study day, relative to first dose, mean (SD)	.989	41.11 (24.42)	41.16 (23.47)
ODV concentration, mean (SD), ng/mL	< .001	221.37 (169.32)	109.97 (94.55)
Venlafaxine concentration, mean (SD), ng/mL	< .001	77.08 (78.54)	276.76 (234.01)
Total concentration (ODV + venlafaxine), mean (SD), ng/mL	.056	298.44 (232.72)	386.73 (305.85)

Abbreviations: EM = extensive metabolizer, ODV = O-desmethylvenlafaxine, PM = poor metabolizer.

Dose and Plasma Concentrations

There was no significant difference between EMs and PMs in raw mean venlafaxine dose (Table 2). Consistent with the criteria used to determine metabolizer status, EMs and PMs had statistically significant differences in mean plasma concentrations of ODV and venlafaxine ($P < .001$ for both). The difference in total (ODV + venlafaxine) concentrations between EMs and PMs approached significance, tending to be higher in the PMs.

Efficacy

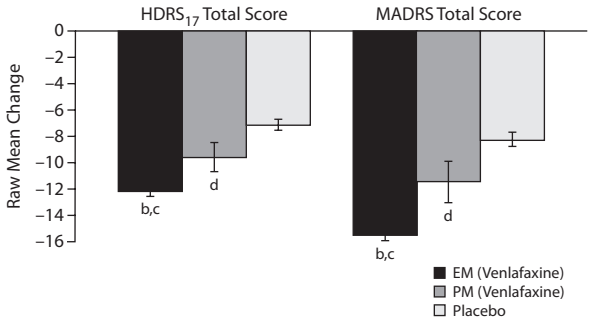
Venlafaxine demonstrated efficacy in treating MDD in both EM and PM patients compared with placebo. Both EM and PM venlafaxine-treated patients had statistically greater changes from baseline on the $HDRS_{17}$, $HDRS_6$, the MADRS, and the CGI-S scale and significantly greater improvement on the CGI-I scale compared with the placebo group (all comparisons, $P \leq .037$).

Patients classified as EMs demonstrated significantly greater improvement compared with PM patients on all but 1 of the scales after venlafaxine treatment. A statistically significant difference was observed between EMs and PMs on the primary outcome measure, mean change from baseline on the $HDRS_{17}$ total score (–12.22 and –9.55, respectively; $P = .010$). Significant differences between EMs and PMs also were observed for the $HDRS_6$ score (–7.43 and –5.76, respectively; $P = .008$), the MADRS total score (–15.43 and –11.45, respectively; $P = .008$), and the CGI-I score (1.91 and 2.39, respectively; $P = .020$). EMs experienced a numerically greater reduction in CGI-S scores compared with PMs, but the difference did not reach statistical significance (–1.80 and –1.49, respectively; $P = .094$). Mean change from baseline in $HDRS_{17}$ and MADRS total scores for EM, PM, and placebo groups is shown in Figure 1A.

Rates of response and remission varied significantly with metabolizer status. Response rates based on the CGI-I scale and the $HDRS_{17}$, and MADRS were 76%, 65%, and 61%, respectively, for EMs compared with 57%, 45%, and 39%, respectively, for PMs (all comparisons, $P \leq .012$). Extensive metabolizers had significantly higher rates of MADRS remission compared with PMs (56% and 37%, respectively; $P = .015$); $HDRS_{17}$ remission rates did not differ statistically between the 2 groups (41% and 29%, respectively). Placebo response rates on the CGI-I scale, and the $HDRS_{17}$ and the MADRS were 39%, 32%, and 29%, respectively; remission rates for $HDRS_{17}$ and MADRS scales were 21% and 27%, respectively. Differences from placebo were significant for EMs with all definitions of response (CGI-I, odds ratio [OR]: 4.86 [3.57, 6.60]; $HDRS_{17}$, OR: 3.93 [2.92, 5.29]; MADRS, OR: 3.86 [2.86, 5.22]) and remission ($HDRS_{17}$, OR: 2.70 [1.96, 3.72]; MADRS, OR: 3.41 [2.52, 4.62]; all comparisons, $P < .001$). For PMs, only the difference from placebo on CGI-I response was statistically significant (OR 2.06 [1.12, 3.76]; $P = .021$). $HDRS_{17}$ and MADRS response and remission rates are displayed in Figure 1B.

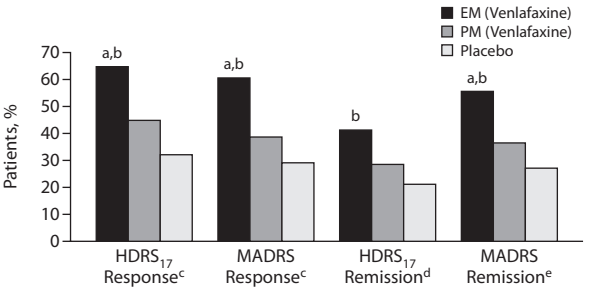
There was no linear correlation between plasma venlafaxine or ODV concentrations, venlafaxine + ODV, or the ODV/venlafaxine ratio and improvement on any of the continuous efficacy measures (Pearson *r* ranged from –0.09724 to 0.02427). Likewise, there was no association between plasma levels and response (using the $HDRS_{17}$ definition); there were no statistically significant differences in plasma concentrations of ODV (220 ng/mL vs 192 ng/mL), venlafaxine (97 ng/mL vs 100 ng/mL), ODV + venlafaxine (317 ng/mL vs 292 ng/mL), or ODV/venlafaxine ratio (3.90 vs 3.74) between $HDRS_{17}$ responders and nonresponders.

Figure 1A. Change in Scores on the $HDRS_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status[a]



[a]Error bars represent the SD.
[b]*P* value ≤ .01, EM vs PM.
[c]*P* value < .001, EM vs placebo.
[d]*P* value < .04, PM vs placebo.

Figure 1B. Response and Remission Rates Based on the $HDRS_{17}$ and MADRS in Patients With Major Depression Treated With Venlafaxine or Placebo, by Metabolizer Status



[a]*P* value < .02, EM vs PM.
[b]*P* value < .001, EM vs placebo.
[c]Response is defined as ≥ 50% decrease from baseline score.
[d]$HDRS_{17}$ remission is defined as total score ≤ 7.
[e]MADRS remission is defined as total score ≤ 12.

Abbreviations: EM = extensive metabolizer, $HDRS_{17}$ = 17-item Hamilton Rating Scale for Depression, MADRS = Montgomery-Asberg Depression Rating Scale, PM = poor metabolizer.

Table 3. Discontinuations in 836 Patients With Major Depressive Disorder Treated With Venlafaxine or Placebo, by Primary Reason[a]

Reason for Discontinuation[a]	Overall *P* Value[b]	EM vs PM *P* Value	Venlafaxine EM (n = 415), n (%)	Venlafaxine PM (n = 49), n (%)	Placebo (n = 372), n (%)	Total (n = 836), n (%)
All discontinuations	< .001	.839	69 (16.6)	7 (14.3)	144 (38.7)	220 (26.3)
Adverse reaction	.926	1.000	18 (4.3)	2 (4.1)	18 (4.8)	38 (4.5)
Failed to return	< .001	.238	17 (4.1)	0 (0)	45 (12.1)	62 (7.4)
Other medical event	.393	.361	3 (0.7)	1 (2.0)	4 (1.1)	8 (1.0)
Other nonmedical event	.201	.285	2 (0.5)	1 (2.0)	5 (1.3)	8 (1.0)
Patient/subject request	.028	1.000	3 (0.7)	0 (0)	12 (3.2)	15 (1.8)
Protocol violation	.237	1.000	3 (0.7)	0 (0)	8 (2.2)	11 (1.3)
Unsatisfactory response/lack of efficacy	< .001	.747	23 (5.5)	3 (6.1)	52 (14.0)	78 (9.3)

[a]Total discontinued is the sum of individual reasons because they are mutually exclusive by subject.
[b]Fisher exact test *P* value (2-tailed).
Abbreviations: EM = extensive metabolizer, PM = poor metabolizer.

Safety

Reasons for discontinuation. Overall discontinuation rates were 16.6% and 14.3% for venlafaxine-treated EM and PM patients, respectively, versus 38.7% for placebo-treated patients (*P* < .001 overall); 4.3% of EMs and 4.1% of PMs discontinued due to adverse events (AEs; placebo, 4.8%). Neither overall discontinuation rate nor the rate of discontinuations due to AEs differed significantly between EMs and PMs (Table 3).

Adverse events. The overall rate of TEAEs did not significantly differ between EMs (93.5%) and PMs (98.0%). There were statistically significant differences between EMs and PMs in the percentage of patients with increased alkaline phosphatase (1/415 [0.2%] and 2/49 [4.1%], respectively; *P* = .031), sweating (55/415 [13.3%] and 12/49 [24.5%]; *P* = .050), and insomnia (93/415 [22.4%] and 19/49 [38.8%]; *P* = .020). No other significant differences were observed.

DISCUSSION

The findings presented here demonstrate differences between EMs and PMs in antidepressant response to venlafaxine. Although venlafaxine-treated patients, whether EMs or PMs, experienced significantly greater improvement compared with placebo-treated patients, venlafaxine-treated EM patients scored significantly better than venlafaxine-treated PM patients on a wide range of efficacy measures (ie, the $HDRS_{17}$, the $HDRS_6$, the MADRS, and the CGI-I scale). The difference in efficacy of venlafaxine for EMs vs PMs is in the range of the differences demonstrated for active treatment over placebo in antidepressant studies.[25,26] After subtracting the placebo response and remission rates, venlafaxine-treated EM patients achieved 2- to 3-fold higher rates of response and remission compared with venlafaxine-treated PM patients at comparable doses. These results strongly implicate the CYP2D6 phenotype as a determinant of the likelihood of a robust antidepressant response to venlafaxine. Since there were no important differences between EMs and PMs in terms of venlafaxine dose or tolerability, these factors are not likely to account for the difference in efficacy findings.

There are several possible explanations for our findings, including some potential confounding factors. PM status has been associated with higher rates of AEs or discontinuations due to AEs in several studies (although not in all of them[27]) investigating the effects of the CYP2D6 phenotype

on antidepressant response.[9,14,15] However, the overall rates of AEs and discontinuations due to AEs did not differ between EMs and PMs in this study, even though there was a significantly higher occurrence of several specific AEs (increased alkaline phosphatase, sweating, and insomnia) in PMs compared with EMs. Further, dose reduction in PMs in response to poor tolerability did not account for the difference in efficacy demonstrated in this study, as there were no significant differences between CYP2D6 phenotype groups in mean venlafaxine dose or time to reach target dose.

EMs and PMs might vary in their response to venlafaxine because they are exposed to different plasma levels of venlafaxine and ODV. Significant differences in plasma concentrations of ODV and venlafaxine for EMs versus PMs are expected, as phenotype status was determined based on the ODV/venlafaxine ratio. However, there was no statistical correlation between drug plasma concentrations and efficacy outcomes, including change from baseline $HDRS_{17}$ scores or responder status. Several studies have reported the lack of a relationship between plasma drug concentrations and efficacy measures for antidepressants of different classes,[13,28–31] including venlafaxine.[32] Multiple factors contribute to the complexity of the relationship between plasma concentrations and efficacy of antidepressants. These include differences between plasma drug concentration and concentration at the site of action, saturation of efficacy at higher drug doses, the substantial number of patients who improve irrespective of the dosage received (placebo effect), and individual differences in drug responsiveness.[33,34] Although an apparent association between plasma drug levels and efficacy was not detected, this study demonstrates a clear relationship between CYP2D6 phenotype and efficacy. One possible explanation is that ODV may be primarily responsible for the therapeutic effects of venlafaxine, and venlafaxine itself may be associated with more AEs.

In addition to the CYP2D6 pathway, venlafaxine is also metabolized in humans by CYP3A4 (with CYP2C19 and CYP2C9 contributing) to the minor metabolite N-desmethylvenlafaxine (NDV).[8,35] This minor pathway is more important in PMs, who have significantly higher levels of NDV compared with EMs and ultrarapid metabolizers.[36] NDV has shown some serotonin reuptake inhibition relative to venlafaxine in vitro, but no in vivo activity.[37] It is unclear what role this minor metabolite could play in the diminished efficacy of the parent compound in PMs. NDV was not measured in this study.

Another possible explanation for the efficacy differences seen in this analysis is that a patient's CYP2D6 genotype plays an important role in determining antidepressant efficacy, beyond the known effects of the genotype on venlafaxine metabolism. The CYP2D6 enzyme has been localized outside the gut and liver, in multiple brain areas, including the neocortex, hippocampus, and hypothalamus.[38] The CYP2D6 enzyme has been shown to be involved in regeneration of serotonin from an endogenous substrate, 5-methoxytryptamine (5MT).[39] The regeneration of serotonin from 5MT may be impaired in PMs, resulting in a subtle decrease in serotonergic, and possibly dopaminergic, activity.[40] The one study that examined CYP2D6 phenotype (based on dextromethorphan metabolic ratio) found no association between metabolizer status and treatment response.[31] Conversely, Mihara and colleagues[41] reported that responder rates were related to a particular range of plasma mianserin concentrations in depressed patients and that both plasma drug levels and responder rates were associated with CYP2D6 genotype. Differences between EMs and PMs on personality assessment scores related to impulsivity and alertness have also been reported.[42]

There are limitations to this study. First, although no significant differences in efficacy were observed between the IR and ER formulations, and the distribution of IR and ER formulation was comparable among EMs and PMs, formulation differences may have had an impact on some plasma concentration parameters. Second, limitations in the decision rules for classifying patients into only 2 phenotype groups may have prevented clear separation between EMs and PMs, because patients who could have been considered intermediate or ultrarapid metabolizers were placed into the EM group. Third, the absence of correction for multiple comparisons may have increased the likelihood of false positive errors.

Despite the acknowledged limitations, antidepressant response to venlafaxine clearly varies with CYP2D6 metabolizer phenotype. Thus, this phenotype is one factor to consider in patients who have a poor response to antidepressant treatment with venlafaxine, and possibly other antidepressants. There have been a number of published reports of specific genetic differences, including effects of serotonin, norepinephrine, or dopamine transporter gene polymorphisms[43–46] and polymorphisms in catechol-O-methyltransferase[47,48] and monoamine oxidase B,[49] affecting antidepressant response to drugs from several classes of antidepressants. This study is the first to rigorously establish the role of the CYP2D6 phenotype in the determination of antidepressant responsiveness.

Drug name: venlafaxine (Effexor and others).
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REFERENCES

1. Zanger UM, Raimundo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Naunyn Schmiedebergs Arch Pharmacol*. 2004;369(1):23–37.
2. Ingelman-Sundberg M. Pharmacogenetics of cytochrome P450 and its applications in drug therapy: the past, present and future. *Trends Pharmacol Sci*. 2004;25(4):193–200.
3. de Leon J, Armstrong SC, Cozza KL. Clinical guidelines for psychiatrists for the use of pharmacogenetic testing for CYP450 2D6 and CYP450 2C19. *Psychosomatics*. 2006;47(1):75–85.
4. Bradford LD. CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants. *Pharmacogenomics*. 2002;3(2):229–243.
5. Gaedigk A, Bradford LD, Marcucci KA, et al. Unique CYP2D6 activity distribution and genotype-phenotype discordance in black Americans. *Clin Pharmacol Ther*. 2002;72(1):76–89.
6. Gaedigk A. Interethnic differences of drug-metabolizing enzymes. *Int J Clin Pharmacol Ther*. 2000;38(2):61–68.
7. Bradford LD, Kirlin WG. Polymorphism of CYP2D6 in black populations: implications for psychopharmacology. *Int J Neuropsychopharmacol*. 1998;1(2):173–185.
8. Otton SV, Ball SE, Cheung SW, et al. Venlafaxine oxidation in vitro is catalysed by CYP2D6. *Br J Clin Pharmacol*. 1996;41(2):149–156.
9. Shams ME, Arneth B, Hiemke C, et al. CYP2D6 polymorphism and clinical effect of the antidepressant venlafaxine. *J Clin Pharm Ther*. 2006;31(5):493–502.
10. Veefkind AH, Haffmans PM, Hoencamp E. Venlafaxine serum levels and CYP2D6 genotype. *Ther Drug Monit*. 2000;22(2):202–208.
11. Nichols AI, Lobello K, Guico-Pabia C, et al. Venlafaxine metabolism as a marker of cytochrome P450 enzyme 2D6 metabolizer status. *J Clin Psychopharmacol*. 2009;29(4):383–386.
12. Borgherini G, Conforti D, Scarso C, et al. Is it possible to early predict venlafaxine response in major depression? [poster]. Presented at the 16th Congress of the European College of Neuropsychopharmacology; September 20–24, 2003; Prague, Czech Republic
13. Grasmäder K, Verwohlt PL, Rietschel M, et al. Impact of polymorphisms of cytochrome-P450 isoenzymes 2C9, 2C19 and 2D6 on plasma concentrations and clinical effects of antidepressants in a naturalistic clinical setting. *Eur J Clin Pharmacol*. 2004;60(5):329–336.
14. McAlpine DE, O'Kane DJ, Black JL, et al. Cytochrome P450 2D6 genotype variation and venlafaxine dosage. *Mayo Clin Proc*. 2007; 82(9):1065–1068.
15. Rau T, Wohlleben G, Wuttke H, et al. CYP2D6 genotype: impact on adverse effects and nonresponse during treatment with antidepressants—a pilot study. *Clin Pharmacol Ther*. 2004;75(5):386–393.
16. Rudolph RL, Fabre LF, Feighner JP, et al. A randomized, placebo-controlled, dose-response trial of venlafaxine hydrochloride in the treatment of major depression. *J Clin Psychiatry*. 1998;59(3):116–122.
17. Cunningham LA. Once-daily venlafaxine extended release (XR) and venlafaxine immediate release (IR) in outpatients with major depression. Venlafaxine XR 208 Study Group. *Ann Clin Psychiatry*. 1997;9(3): 157–164.
18. Thase ME. Efficacy and tolerability of once-daily venlafaxine extended release (XR) in outpatients with major depression. The Venlafaxine XR 209 Study Group. *J Clin Psychiatry*. 1997;58(9):393–398.
19. Mendels J, Johnston R, Mattes J, et al. Efficacy and safety of bid doses of venlafaxine in a dose-response study. *Psychopharmacol Bull*. 1993; 29(2):169–174.
20. Hamilton M. Hamilton Rating Scale for Depression (Ham-D). In: Rush AJ, Pincus HA, First MB, et al, eds. *Handbook of Psychiatric Measures*. 1st ed. Washington, DC: American Psychiatric Association; 2000:526–529.
21. Bech P, Gram LF, Dein E, et al. Quantitative rating of depressive states. *Acta Psychiatr Scand*. 1975;51(3):161–170.
22. Montgomery SA, Åsberg M. A new depression scale designed to be sensitive to change. *Br J Psychiatry*. 1979;134(4):382–389.
23. Guy W. *ECDEU Assessment Manual for Psychopharmacology.* US Dept Health, Education, and Welfare publication ADM 76-338. Rockville, Md: National Institute of Mental Health; 1976:217–222.
24. Flockhart DA. Drug Interactions: Cytochrome P450 Drug Interaction Table. http://medicine.iupui.edu/flockhart/table.htm. Accessed May 22, 2008.
25. Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *Br J Psychiatry*. 2001;178(3):234–241.
26. Stahl SM, Entsuah R, Rudolph RL. Comparative efficacy between venlafaxine and SSRIs: a pooled analysis of patients with depression. *Biol Psychiatry*. 2002;52(12):1166–1174.
27. Whyte EM, Romkes M, Mulsant BH, et al. CYP2D6 genotype and venlafaxine-XR concentrations in depressed elderly. *Int J Geriatr Psychiatry*. 2006;21(6):542–549.
28. Montgomery SA, Roy D, Wynne-Willson S, et al. Plasma levels and clinical response with imipramine in a study comparing efficacy with mianserin and nomifensine. *Br J Clin Pharmacol*. 1983;15(suppl 2): 205S–211S.
29. Kasper S, Dötsch M, Kick H, et al. Plasma concentrations of fluvoxamine and maprotiline in major depression: implications on therapeutic efficacy and side effects. *Eur Neuropsychopharmacol*. 1993;3(1):13–21.
30. Ilett KF, Blythe TH, Hackett LP, et al. Plasma concentrations of dothiepin and its metabolites are not correlated with clinical efficacy in major depressive illness. *Ther Drug Monit*. 1993;15(5):351–357.
31. Spina E, Gitto C, Avenoso A, et al. Relationship between plasma desipramine levels, CYP2D6 phenotype and clinical response to desipramine: a prospective study. *Eur J Clin Pharmacol*. 1997;51(5):395–398.
32. Gex-Fabry M, Balant-Gorgia AE, Balant LP, et al. Time course of clinical response to venlafaxine: relevance of plasma level and chirality. *Eur J Clin Pharmacol*. 2004;59(12):883–891.
33. Preskorn SH. To monitor or not to monitor? *J Pract Psych Behav Hlth*. 1996;2(3):172–175.
34. Preskorn SH. To monitor or not to monitor, II: the glass is more than half full. *J Pract Psychiatry Behav Health*. 1996;2(5):307–310.
35. Fogelman SM, Schmider J, Venkatakrishnan K, et al. O- and N-demethylation of venlafaxine in vitro by human liver microsomes and by microsomes from cDNA-transfected cells: effect of metabolic inhibitors and SSRI antidepressants. *Neuropsychopharmacology*. 1999;20(5):480–490.
36. Hermann M, Hendset M, Fosaas K, et al. Serum concentrations of venlafaxine and its metabolites O-desmethylvenlafaxine and N-desmethylvenlafaxine in heterozygous carriers of the CYP2D6*3, *4 or *5 allele. *Eur J Clin Pharmacol*. 2008;64(5):483–487.
37. Muth EA, Moyer JA, Haskins JT, et al. Biochemical, neurophysiological, and behavioral effects of Wy-45,233 and other identified metabolites of the antidepressant venlafaxine. *Drug Dev Res*. 1991;23(2):191–199.
38. Siegle I, Fritz P, Eckhardt K, et al. Cellular localization and regional distribution of CYP2D6 mRNA and protein expression in human brain. *Pharmacogenetics*. 2001;11(3):237–245.
39. Yu AM, Idle JR, Byrd LG, et al. Regeneration of serotonin from 5-methoxytryptamine by polymorphic human CYP2D6. *Pharmacogenetics*. 2003;13(3):173–181.
40. Ozdemir V, Gunes A, Dahl ML, et al. Could endogenous substrates of drug-metabolizing enzymes influence constitutive physiology and drug target responsiveness? *Pharmacogenomics*. 2006;7(8):1199–1210.
41. Mihara K, Otani K, Tybring G, et al. The CYP2D6 genotype and plasma concentrations of mianserin enantiomers in relation to therapeutic response to mianserin in depressed Japanese patients. *J Clin Psychopharmacol*. 1997;17(6):467–471.
42. Bertilsson L, Alm C, De Las Carreras C, et al. Debrisoquine hydroxylation polymorphism and personality. *Lancet*. 1989;1(8637):555.
43. Kang RH, Wong ML, Choi MJ, et al. Association study of the serotonin transporter promoter polymorphism and mirtazapine antidepressant response in major depressive disorder. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(6):1317–1321.
44. Kim H, Lim SW, Kim S, et al. Monoamine transporter gene polymorphisms and antidepressant response in Koreans with late-life depression. *JAMA*. 2006;296(13):1609–1618.
45. Kirchheiner J, Nickchen K, Sasse J, et al. A 40-basepair VNTR polymorphism in the dopamine transporter (DAT1) gene and the rapid response to antidepressant treatment. *Pharmacogenomics J*. 2007;7(1):48–55.
46. Yoshida K, Takahashi H, Higuchi H, et al. Prediction of antidepressant response to milnacipran by norepinephrine transporter gene polymorphisms. *Am J Psychiatry*. 2004;161(9):1575–1580.
47. Yoshida K, Higuchi H, Takahashi H, et al. Influence of the tyrosine hydroxylase val81met polymorphism and catechol-O-methyltransferase val158met polymorphism on the antidepressant effect of milnacipran. *Hum Psychopharmacol*. 2008;23(2):121–128.
48. Szegedi A, Rujescu D, Tadic A, et al. The catechol-O-methyltransferase Val108/158Met polymorphism affects short-term treatment response to mirtazapine, but not to paroxetine in major depression. *Pharmacogenomics J*. 2005;5(1):49–53.
49. Tadić A, Rujescu D, Müller MJ, et al. A monoamine oxidase B gene variant and short-term antidepressant treatment response. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(7):1370–1377.