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PharmGKB summary: venlafaxine pathway

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Keywords

CYP2C19; CYP2D6; pharmacogenetics; serotonin–norepinephrine reuptake inhibitor; venlafaxine

Introduction

Venlafaxine (VEN) is a serotonin–norepinephrine reuptake inhibitor marketed for the treatment of depression disorders. The molecular targets of VEN are the solute carrier family 6 (neurotransmitter transporter, serotonin), member 4 (SLC6A4), and solute carrier family 6 (neurotransmitter transporter, noradrenalin), member 2 (SLC6A2), resulting in an inhibition of serotonin and noradrenalin reuptake from the synaptic cleft. VEN also slightly inhibits dopamine reuptake. Therefore, those substances are available prolonged in the synaptic cleft for serotonergic and noradrenergic neurotransmission.

VEN consists of a racemic mixture of *R*(+) and *S*(−) enantiomer. The (*R*) enantiomer has been shown to show greater serotonin reuptake inhibition property, whereas the (*S*) enantiomer inhibits the reuptake of both monoamines [1,2].

Pharmacokinetics

VEN is highly metabolized in humans, with a urinary excretion of the unchanged compound between 1 and 10% of an administered dose [3,4]. Demethylation to *O*-desmethylvenlafaxine (ODV) is the primary route of the first pass metabolism of VEN. Cytochrome P450 2D6 (CYP2D6) is the major enzyme involved in ODV formation (Fig. 1) [5,6]. ODV is excreted unchanged and as its glucuronide [3].

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Conflicts of interest

There are no conflicts of interest.

A few studies have described a possible stereoselective metabolism of VEN to ODV with either selection toward the (*S*) isoform [4,5] or the (*R*) isoform [7,8], but the majority of studies on VEN pharmacokinetics and antidepressant response in association with the CYP2D6 metabolizer phenotype do not distinguish between the enantiomers (Table 1).

ODV has antidepressant activity and desvenlafaxine succinate, a salt of ODV, is an FDA-approved drug [34]. Despite the predominant role of CYP2D6, ODV plasma concentrations are detectable in CYP2D6 poor metabolizer (PM) individuals who lack CYP2D6 activity (Table 1), which suggests that other cytochrome P450 enzymes might be involved in ODV production to a minor extent [19]. In-vitro experiments suggest that CYP2C19 may be involved in the formation of ODV in human liver microsomes [6].

N-Demethylation of VEN to *N*-desmethylvenlafaxine (NDV) is generally a minor metabolic pathway and is catalyzed by CYP3A4 and CYP2C19 [6]. NDV is found at about 1% in urine and has weak serotonin and noradrenaline reuptake inhibition properties *in vitro* [4]. Patients with the CYP2D6 PM phenotype show a higher level of NDV compared with CYP2D6 extensive metabolizer (EM) patients, implicating an increase in flux through this route when ODV production is reduced [14,18,19,25].

ODV and NDV are further metabolized by CYP2C19, CYP2D6, and/or CYP3A4 into *N,O*-didesmethylvenlafaxine, which is a minor metabolite with no known pharmacological effect [2,24]. *N,O*-didesmethylvenlafaxine is itself metabolized into *N,N,O*-tridesmethylvenlafaxine or excreted as its glucuronide [3]. To our knowledge, no studies have reported the UGT enzymes responsible for glucuronidation.

The effect of CYP2C19 in VEN metabolism is not well understood [21,28], and further studies are needed. As both PM and ultrarapid metabolizer (UM) variations of CYP2C19 are present in most populations, it is reasonable to expect that these may have an impact on VEN metabolism, particularly in CYP2D6 PM and intermediate metabolizer (IM).

The therapeutic range of VEN+ODV in blood is between 125 and 400 µg/l [19,35,36]. However, a number of studies report a poor relationship between efficacy and plasma drug levels and more research is needed [36,37]. There is a correlation between early response and the sum of the VEN+ODV concentration but comparison of overall response and nonresponse suggests no effect of VEN pharmacokinetic on long-term response [37].

Transport

Studies of knockout mice suggest that VEN is a substrate of the multiple drug resistance protein 1 (MDR1, P-gp) encoded by *ABCB1* [38,39]. Further, in-vitro studies showed that VEN but not ODV is an inducer of *ABCB1* and breast cancer resistance protein (*BCRP*) expression [40]. Both only minimal inhibit MDR1 activity [41].

Adverse effects

A withdrawal syndrome can occur after the discontinuation of selective serotonin reuptake inhibitors (SSRIs), particularly those with a relatively shorter half-life such as paroxetine.

This can also occur when discontinuing VEN and tapering is sometimes recommended [42–44]. A placebo-controlled study shows a significantly higher number of adverse events after VEN treatment discontinuation than after discontinuation of a placebo [45].

In case studies, adverse reactions are reported in association with a very high VEN plasma concentration; the most common symptoms are neurotoxicity and cardiovascular toxicity [12,18,46,47]. High VEN concentrations can occur from overdose of VEN and/or a CYP2D6 PM genotype and/or the concomitant presence of other CYP2D6 substrates.

Hyponatremia [48,49] and rhabdomyolysis can also occur [50].

Pharmacogenomics

Treatment outcome for antidepressants is variable, and there is considerable interest in establishing predictors for response or adverse effects.

The pharmacokinetics of VEN is clearly affected by the CYP2D6 metabolizer phenotype and a correlation exists between the *CYP2D6* genotype and the metabolic ratio of VEN to ODV (Table 1). CYP2D6 PM have higher VEN, lower ODV, and consequently higher NDV plasma concentrations [19,21,26].

Only a few small studies ($n = 25$ –464) and case reports have investigated the effect of *CYP2D6* variants on VEN response or the risk of adverse reaction during VEN treatment. In general, little is known about the relationship between drug plasma level and efficacy or tolerability.

One study used VEN as a phenotyping probe to classify PM and extensive metabolizer (EM) also found an influence on VEN treatment efficacy [10]. This study represented a secondary analysis of the VEN and ODV plasma levels from the four double-blind, placebocontrolled trials that were part of the VEN approval process. The results show that VEN is more effective than placebo in CYP2D6 EM but not in CYP2D6 PM (Table 1) [10]. The discontinuation rate, side-effect rate, and VEN dose were not different between PM and EM [10]. In general, an ODV/VEN ratio below 1 seems to map to genotypically PM patients, although some patients with the EM genotype show an ODV/VEN ratio below 1 [14].

An earlier study in a smaller cohort ($n=33$) showed that response was associated with a higher ODV/VEN ratio among EM (ODV/VEN ratio in responder: 3.7–8.9 and nonresponder: 1.5–3.5) [19]. The study only included three PM and two UM patients and could not establish a relationship between higher VEN concentration and an increased likelihood of side effects or treatment response [19]. In contrast, other studies have not been able to link VEN response with ODV and VEN plasma levels or the *CYP2D6* genotype [11,14,15]. An accompanying editorial proposes that CYP2D6 PM patients are less responsive to VEN because CYP2D6 has pharmacodynamics effects on the metabolism of serotonin in the brain [51].

Cases of severe arrhythmias have been reported in four patients treated with VEN who were all CYP2D6 PMs [18]. A higher risk for side effects may exist in individuals lacking

CYP2D6 activity and thus with elevated VEN concentrations [14,16]. This may be because of pharmacological differences between VEN and ODV [14], although other studies show no differences in the risk of side effects [10,15]. Five patients with the intermediate CYP2D6 metabolizer phenotype (IM), who lack a fully active *CYP2D6* allele, could not tolerate VEN doses above 75 mg/day and all except one discontinued the VEN treatment because of intolerable side effects [13]. The clinical data for this study were retrieved from electronic clinical records and therefore no VEN and ODV plasma concentrations were available [13].

Differences in the clinical efficacy of antidepressants that are substrates of MDR1 including VEN were associated with *ABCB1* variations (rs2235067, rs4148740, rs10280101, rs7787082, rs2032583, rs4148739, rs11983225, rs10248420, rs2235040, rs12720067, and rs2235015) in a candidate gene association study [52]. These studies suggest a possible influence of intronic SNPs on regulatory elements of the gene that may modulate the antidepressant distribution into the brain. These findings need to be verified. An analysis of the distribution of *ABCB1* SNPs (rs2229109, rs1128503, rs2032582, and rs1045642) in 116 VEN-positive post-mortem cases indicated that rs1128503 ($P=0.0173$) and rs1045642 ($P=0.0074$) showed significant differences in allele frequencies between the intoxication cases and the nonintoxication cases [53]. Homozygous carriage of the T allele was less frequent in intoxication cases compared with nonintoxication cases [53].

Only a few candidate gene studies have investigated the influence of variants in pharmacodynamic genes such as catechol-*O*-methyltransferase (*COMT*) gene, serotonin receptor 2A (*HTR2A*) gene, brain-derived neurotrophic factor (*BDNF*) gene, FK506 binding protein 5 (*FKBP5*) gene, and dopamine transporter (*SLC6A3*) gene on the variability of treatment outcomes.

A cohort of 156 patients with generalized anxiety disorder, with a population of 112 European-American and 41 African-Americans and three others, was treated with VEN for 6 months with a flexible dose of 75–225 mg/day as phase I of an 18-month relapse prevention study. The primary outcome analysis was defined as a reduction of 50% or more in the Hamilton Anxiety Scale (HAM-A) score at 6 months and remission with a HAM-A score of 7 or below. The secondary outcome measurement was the Clinical Global Impression of Improvement (CGI-I) score, with improvement defined as a CGI-I of 1 and 2 [54–56]. Overall, no significant association between the primary outcome measure and the rs4680 variant (Val158Met) in the *COMT* gene could be established in the 112 European-American patients of this cohort [54]. However, a slight dominant effect of the A-allele (Met) compared with the G allele (Val) is shown when the CGI-I scale is used as secondary outcome measure [54]. In the same cohort of 156 anxious patients, a trend of association was found for the *HTR2A* rs7997012 G allele with a difference in frequency between responders (70%) and nonresponders (56%) at 6 months ($P=0.05$) using the HAM-A score as described above [55]. Furthermore, the G allele was associated with improvement using the CGI-I as the secondary outcome measure ($P=0.001$, odds ratio=4.72) [55]. Treatment response in association with the functional variant rs6265 (Val66Met) in the *BDNF* gene was assessed in 111 of the European-American patients and no significant correlation was found [56].

In studies that investigated predictors of the response to antidepressant therapy, VEN was included along with SSRIs and tricyclic antidepressants (TCAs) [57,58]. *FKBP5* variants rs3800373 and rs1360780, which are in linkage, were associated with a higher response rate ($P = 0.004$, odds ratio 1.8; 95% confidence interval: 0.98–3.3) primarily in the subgroups of patients receiving antidepressant combinations or VEN [58]. The *SLC6A3* 3'-UTR variable number of tandem repeats (VNTR) SNP influenced rapid response to antidepressant therapy, defined as an improvement in depression symptoms during the 3 weeks after treatment initiation (39 of 190 patients were treated with VEN). The study participants were either homozygous carrier for the 9 or 10-repeat genotype or heterozygous carriers for the 9- and 10-repeat genotypes [57]. The number of rapid responders was smaller among homozygous carriers of the 9-repeat allele than among patients carrying the 10-repeat allele [57]. This effect was significant when all antidepressants were combined ($P = 0.0037$). Analyses of the individual drug groups only reached statistical significance for the patients receiving SSRIs [57].

Conclusion

An influence of *CYP2D6* variations on the pharmacokinetic parameters of VEN is clearly shown in a large number of studies. The higher VEN and reduced ODV concentrations in *CYP2D6* PM patients seem to translate into reduced response and a higher risk of side effects compared with EM carriers. However, the studies on VEN treatment outcome are limited in sample size and there are conflicting results. Larger studies are needed to study sufficient numbers of PM, IM, and UM to determine whether the effect of *CYP2D6* variations on VEN and ODV plasma levels translates into an increased risk for nonresponse and side effects. Furthermore, the inclusion of the *CYP2C19* genotype may help to understand the variability in VEN response. Finally, further investigation of the VEN and ODV mechanism of action (including binding preferences of the respective enantiomers) might be useful in explaining pharmacological differences. A preference of *CYP2D6* for the *S* or the *R* form might also affect the overall monoamine reuptake profile. Therefore, improved understanding of the substrate selectivity of *CYP2D6* might aid in the understanding of the complex issue of VEN drug response and side-effect profile.

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Fig. 1.

Stylized cells showing the metabolism and mechanism of action of venlafaxine. A fully interactive version is available at PharmGKB <http://www.pharmgkb.org/pathway/PA166014758>.

Table 1
Influence of genetic variations in *CYP2D6* on VEN metabolism and drug response

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
<i>Studies that investigate association of CYP2D6 phenotype with VEN response</i>							
EM (157); IM (17); PM (2); UM (8)	*1/*1 (69); *1/*3 (2); *1/*4 (47); *1/*5 (6); *1/*10 (10); *1/*17 (2); *1/*41 (19); *1×2/*41 (2); *1×2/*10 (1); *3/*41 (1); *4/*10 (3); *4/*41 (4); *10/*10 (3); *10/*41 (2); *41/*41 (3); *3/*4 (1); *4/*4 (1); *1×2/*1 (7); *1×4/*1 (1)	184 (OCD patients)	Mixed	Not reported		Study evaluates retrospectively participants one or more trials of treatment with antidepressants and multiple antidepressants were included. 53 patients were treated with VEN. No significant impact of CYP2D6 ($P = 0.743$) or CYP2C19 ($P = 0.939$) metabolizer status on overall treatment response was observed. No significant impact was shown for VEN comparing EM with none-EM (UM, IM, PM). No significant impact of CYP2D6 ($P = 0.619$) or CYP2C19 ($P = 0.391$) metabolizer status on occurrence of side effects was observed. Higher rate of side effects to VEN was found in CYP2D6 EM when comparing CYP2D6 EM (24 of 40) with CYP2D6 none-EM (UM,	Brandl <i>et al.</i> [9]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
EM (415); PM (49)	Phenotyping with venlafaxine; patients with ODV/VEN ratios >1 were classified as EM and ratios <1 as PM	464 (366 received placebo)	Not reported	Ranged between 75 and 375 mg/day	Phenotypically EM and PM had significant differences in mean plasma concentrations of ODV and VEN ($P < 0.001$).	IM, PM) (3of 13) ($P = 0.022$). EM showed significantly greater improvement compared with PM after VEN treatment with primary outcome measured with HDRS17 ($P < 0.01$), HDRS6 ($P = 0.008$), MADRS ($P = 0.008$), CGI-I score ($P = 0.02$). Response rate (with CGI-I, HDRS17, MADRS) was higher in EM patients compared with PM patients ($P < 0.012$). Remission rate (MADRS, not other scales) was higher in EM compared with PM ($P = 0.015$). After correcting for placebo EM had two- to three-fold higher rate of response and remission compared with PM. Discontinuation rate and adverse event rate were not different between PM and EM. No differences in VEN dose was found between EM and PM (phenotyped).	Lobello <i>et al.</i> [10]
Two active alleles (17); at least one reduced	Not reported (genotyped for *4, *6, *10, and *41)	39 (OCD patients)	Not reported	Titrated upward to 300 mg/day for 12 weeks	Patients with at least one reduced activity allele have higher VEN levels ($P = 0.018$) and higher	No significant differences when comparing VEN	Van Nieuwerburgh <i>et al.</i> [11]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
activity allele (22)					combined VEN +ODV levels ($P = 0.065$) compared with patients with two active alleles. Patients with at least two reduced activity allele have higher VEN levels ($P < 0.0005$), lower ODV levels ($P = 0.017$), and higher combined VEN+ ODV levels ($P = 0.007$) compared with patients with two active alleles.	response in OCD patients with at least one reduced activity CYP2D6 allele or with two reduced activity CYP2D6 alleles to patients with normal alleles. (Not clear if study included PM or IM; ODV/VEN ratio not reported).	
PM (1)	*4/*4; CYP2C19*1/*1	1	Not reported	225 mg/day VEN plus comedications	Patients presented with tachycardia and agitation. VEN plasma concentration was 1300µg/l and ODV 100 µg/l.	VEN and metoprolol were discontinued. Tachycardia and agitation lessened.	Wijnen <i>et al.</i> [12]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
IM (one inactive plus one reduced activity alleles; 5); EM (at least one fully active allele; 33)	*3/*9 (2); *4/*17 (1); *4/*41 (1); *4/*10 (1); EM not reported	38	Mixed	Varied based on patient 37.5 up to 225 mg/day	-	All IM had maintenance dose not greater than 75 mg/day vs. most of the EM (79%) had a dose of 150 mg/day or more ($P < 0.002$). In one IM an increase in side effects was noticed during attempts to increase the dose above 75 mg/day. In 4 IMs treatment was discontinued because of lack of improvement and/or intolerable side effects. Study was based on medical records; therefore VEN blood levels were not obtained.	McAlpine <i>et al.</i> [13]
PM (4); EM (14); UM (6)	*6/*6 (1); *6/*4 (1); *5/*4 (2); *1/*4 (5); *1/*1 (9); *1xN (6)	25	Not reported	Ranged between 75 and 450 mg/day	CYP2D6 dose-dependent ratio of concentrations was ODV/VEN ratio median = 1.8 (0.3–5.2). PM with two mutant alleles has significantly lower ODV/VEN ratios (0.3, 0.25, 0.25, 0.2) and significantly higher concentration of VEN and NDV (dose corrected) than *1/*1 EM (mean ODV/VEN ratio 3.3±1.9). UM had higher ODV/VEN ratios (mean ratio 10.3±2.7) and significantly lower VEN and NDV concentrations (dose corrected) than EM. Patients with only one active CYP2D6 allele (5 patients with *1/*4 had mean ODV/VEN ratio	PM with ODV/VEN ratio below 0.3 had more side effects (gastrointestinal side effects were the most common) ($P < 0.005$) than EM or UM. No significant difference in therapeutic efficiency observed.	Shams <i>et al.</i> [14]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
					1.1±0.8) had significantly lower metabolic ratios than *1/*1 patients. Sum of VEN and ODV is not different in different CYP2D6 phenotype groups.		
Not reported	*1/*1 (30); [study grouped *1/*4 (13) *4/*4 (3)]	46	Not reported	37.5 mg/day titrated up to 150 mg/day VEN-XR	Elderly patients received several different comedications. No difference in mean VEN dose between the two groups was found. VEN level/dose was significantly higher in the group carrying one or two *4 alleles vs. *1/*1 ($P=0.002$) with a significantly lower ODV concentration ($P=0.02$).	At week 4 CYP2D6 genotype (as compared between the group carrying one or two *4 alleles vs. *1/*1) was not associated with level of depressive symptoms or response to treatment or side effects or rate of study withdrawal (study limitation: dose was not fixed and could be adjusted according to patients' tolerability).	Whyte <i>et al.</i> [15]
PM (1); UM (1) treated with VEN	Not reported	15 total for VEN	Not reported	PM treated with 150mg VEN and several comedications	Study included multiple antidepressants. PM patient on VEN had mean dose-corrected plasma concentration 678% higher than the drug-specific median. UM patient treated with VEN had mean dose-corrected plasma concentration 36% lower than the drug-specific median.	PM patient on VEN showed response (HAM-D and CGI) and experienced side effects. UM patient treated with VEN showed response (HAM-D) but experienced side effects.	Grasmader <i>et al.</i> [16]
Not reported for VEN	Not reported for VEN	6 total for VEN	White	Not reported	-	Study with multiple antidepressants. 3 VEN treated patients were nonresponders but genotype was not broken down by drug. 3 VEN treated patients had	Rau <i>et al.</i> [17]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
PM (2)	*4/*4 (1)	4	Not reported	Varied plus comedication in some cases	-	adverse events but genotype was not broken down by drug. In general the frequency of PM genotype was higher in patient population that experienced adverse events compared with the remaining population ($P < 0.0001$) and the frequency of UM genotype was higher in patient populations that were nonresponders compared with the remaining population ($P = 0.0013$).	Lessard <i>et al.</i> [18]
PM (3); EM (28); UM (2)	*4/*4 (3); *1/*4 (7); *1/*1 (19); CNV (2)	31	White	75 mg/day first week to 225 mg/day in the fourth	VEN levels of the 3 PM patients were significantly higher than those of the EM ($P=0.007$). ODV	4 case studies from the cardiology care center presenting cardiovascular side effects during VEN treatment. 2 patients were PM (identified through genotyping or phenotyping). One patient was phenotypically PM and had many comedication affecting CYP2D6 activity. For the fourth patient no information regarding CYP2D6 metabolizer status is available.	Veefkind <i>et al.</i> [19]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
				week	levels were significantly lower for the PM patients than for the EM ($P = 0.018$). ODV/VEN ratio for PM 0.2, 0.1, 0.1 and ODV/VEN ratio for EM with two or one functional alleles was between 1.5 and 8.9 and ODV/VEN ratio for UM was 15.9 and 13.3. The ratio for responder (in EM and UM group) is clustered between 3.7 and 13.3 and for nonresponder between 1.5 and 3.5. NDV levels in patients with two active alleles were significantly lower than those in patients with one active allele and in PM (two nonfunctional alleles) ($P = 0.001$). Fluctuation in plasma concentration might be influenced by noncompliance over the course of the study. No differences were seen at combined VEN+ ODV levels.	(reduction of more than 50% from baseline HAM-D) were significantly ($P = 0.002$ and 0.031) lower than for nonresponders. None of the PM responded (one was a partial responder), one dropped out because of side effects. One UM responded and one was a nonresponder. 195–400 $\mu\text{g/l}$ for the sum of VEN+ ODV was suggested as the therapeutic range.	
<i>CYP2D6 phenotype – VEN PK association studies</i>							
EM (7); PM (7)	Not reported but PM defined as carrying two nonactive CYP2D6 alleles	14 (healthy individuals)	Predominantly White	50mg ODV or 75mg VEN-ER (single dose)	VEN-ER single dose: C_{max} and AUC for VEN were 180 and 445% higher in PM than EM ($P < 0.01$ for both). C_{max} and AUC for ODV were 434 and 445% higher in EM than PM ($P < 0.001$ for both). Mean ODV/VEN C_{max} ratio is 3.3 and 0.22 for EM and PM. Mean ODV/VENAUC ratio is 6.2 and 0.21 for EM and PM. Desvenlafaxine single dose: C_{max} and AUC were 21 and 10% higher in PM than EM (not statistically significant). 4 PM and 2 EM reported at least one side effect (only included as report; not analyzed).	-	Nichols <i>et al.</i> [20]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
PM (8); EM (81); UM (4)	(*3/*4, *4/*4, *4/*5, *5/*5, *5/*6) = 8; (*1/*1, *1/*2, *1/*4, *1/*5, *1/*6, *1/*9, *1/*10, *2/*2, *2/*3, *2/*4, *2/*5, *2/*9) = 81; (*1/*1xN) = 4	93	Mostly White	Varied between patient, exact dose not reported	Higher numbers of CYP2D6 and CYP2C19 active alleles are associated with lower concentrations of VEN ($P < 0.001$ in a multivariable model that includes dose and both genotypes). Association also for sum of VEN + ODV ($P = 0.021$ for CYP2D6 and $P < 0.001$ for CYP2C19) with VEN + ODV being stronger associated to CYP2C19. No interaction between CYP2D6 and CYP2C19 was found. Higher number of CYP2D6 active alleles tended to have a higher concentration of ODV ($P < 0.001$). CYP2C19 activity score was not found to be significantly associated with ODV concentrations. Highest ODV/VEN ratio is related to highest CYP2D6 activity.	-	McAlpine <i>et al.</i> [21]
UM (5); EM (118); PM (18)	Phenotyping with venlafaxine	141 (healthy individuals)	Indian	37.5 mg up to 150mg (each single dose); IR or XR	Metabolic AUC ODV/VEN ratio is used to distinguish between EM and UM. VEN/ODV ratio is used to distinguish between PM and EM. Regardless of formulation or dose the plasma concentration, the time profiles were distinct among the PM, EM, and UM phenotype.	-	Kandasamy <i>et al.</i> [22]
EM (9); PM (6)	Phenotyped with dextromethorphan	15 (healthy individuals)	Predominantly White	37.5 mg VEN-IR twice per day for 5 days increasing to 75 mg twice per day for 4.5 days	ODV/VEN ratios in EM were 1 or greater and in PM were 0.65 or less 4 h after blood sampling on day 10. One EM had a ratio of 0.65 at 4 h (comedications were excluded from the study).	-	Nichols <i>et al.</i> [23]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
EM (7; 3 with two functional alleles, 4 one functional allele); PM (6)	Not reported	13 (healthy individuals)	White	75 mg VEN-ER	ODV/VEN ratios in EM were greater than 1 and in PM were less than 1 at all sampling times. One PM had a ratio of 1.006 at 72 h blood sample. Phenotyping (see the row above) is in agreement with the genotype results.	-	Nichols <i>et al.</i> [23] (same study as in Preskorn <i>et al.</i> [24])
EM (7; 3 with two functional alleles, 4 one functional allele); PM (7)	Not reported	14	White	75 mg VEN-ER or 100mg desvenlafaxine (single dose)	Mean C_{max} and AUC of VEN were significantly higher in (149 and 331%) in PM patients than in EM patients ($P = 0.001$). PM had prolonged half-life for ODV were significantly lower (78 and 73%) in PM compared with EM ($P = 0.001$) but mean C_{max} and AUC for ODV were comparable between EM and PM after administration of desvenlafaxine. No severe adverse event occurrence was reported during the study.	-	Preskorn <i>et al.</i> [24]
EM (20); HetEM (18); PM (5)	*1/*1 (20); *1/*3 (2); *1/*4 (13); *1/*5 (3); *4/*4 (5)	43	White	Not reported	No difference in sum VEN+ ODV was observed between EM and hetEM but ODV/VEN ratio (AUC) was 50% lower in hetEM (1.5) vs. EM (3.1) (due to a two-fold higher level of VEN in hetEM vs. EM ($P < 0.05$) and the ratio was 0.2 in PM. NDV serum concentration was 5.5-fold ($P < 0.01$) and 22-fold ($P < 0.001$) higher in hetEM and PM vs. EM.	-	Hermann <i>et al.</i> [25]
More than two active alleles (4); 2 active alleles (44); one active allele (32); 0 active allele (4)	Not reported	84	Not reported	Not reported	Significant correlation between the CYP2D6 genotype and metabolic clearance measured as log (VEN/ODV) with values 0.2 correlate with PM (0 active allele) and values < -0.6 correlate with UM (> 2 active alleles), but not a 1 : 1 relationship.	-	Van der Weide <i>et al.</i> [26]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
EM (7); PM (5)	*1/*1 (4); *1/*4 (3); *3/*4 (1); *4/*4 (4)	12	Not reported	18.75 mg twice a day for 2 days	Oral clearance of (R) VEN is nine-fold higher in EMs vs. PMs ($P < 0.005$) but only two-fold higher for (S) VEN ($P < 0.05$).	-	Eap <i>et al.</i> [27]
Not reported	(*1/*1; *1/*2; *2/*2) = group 3 (11); *1/*10; *2/*10 = group 2 (11); *10/*10 = group 1 (5)	28	Japanese	37.5 or 75 or 150 mg (single dose)	C_{max} and AUC of VEN is 298 and 453% higher for group 1 than for group 3 (two CYP2D6 functional alleles) and 91 and 120% higher for group 2 than group 3 ($P < 0.01$). Patients with two loss of function CYP2C19 alleles in group 3 ($n=2$, two CYP2D6 functional alleles) have higher VEN plasma concentration than patients with two loss of function CYP2C19 alleles in group 1 and 2 ($n = 5$).	-	Fukuda <i>et al.</i> [28]
EM (8); PM (6)	Phenotyped with dextromethorphan	14	Not reported	18.85 mg 5 times every 12 h	VEN plasma concentration higher in PM compared with EM ($P < 0.05$), mean oral clearance was four-fold greater in EM compared with PM. NDV in urine was nine-fold higher in PM compared with EM.	-	Lessard <i>et al.</i> [18]
Not reported	*1/*1 (2); *1/*2 (2); *1/*10 (1); *2/*10 (2); *10/*10 (3); *5/*10 (1)	12	Japanese	25 or 37.5 mg (single dose)	Patients carrying the CYP2D6*10 allele have a higher VEN C_{max} and AUC compared with CYP2D6*1/*1 patients. C_{max} and AUC 184 and 484% higher in *5/*10 and *10/*10 patients compared with *1/*1 and *1/*2 patients.	-	Fukuda <i>et al.</i> [29]
<i>Drug intoxication and overdose/poising cases</i>							
CYP2D6 PM and CYP2C19 PM	CYP2D6*4/*5; CYP2C19*2/*2	1	Not reported	150mg VEN twice daily plus comedication	VEN blood concentration of 4.5 mg/kg was detected. ODV/VEN ratio was 0.006 and NDV/VEN ratio was 0.12 which is low. Patient might also have lower CYP3A4 activity (oxycodone, quetiapine, and ethanol).	-	Jornil <i>et al.</i> [30]

CYP2D6 Phenotypes	CYP2D6 diplotypes	Study size	Race/ethnicity	Dose	Findings on venlafaxine pharmacokinetics	Findings on clinical outcomes	References
EM (1)	<i>CYP2D6</i> *1/*5 and <i>CYP2C19</i> *1/*17	1	Not reported	11.25 g	Plasma level was 18015 for VEN and 3846 ng/ml for ODV.	VEN overdose resulting in acute cardiomyopathy.	Vinetti <i>et al.</i> [31]
UM (12); PM (2); EM (111)	Not reported	123 (post-mortem cases positive for VEN in blood screen-18 cases classified as VEN poisoning)	Not reported	NA	Mean VEN concentration 560µg/l, mean ODV concentration 420 µg/l, and NDV concentration 49 µg/l. Presence of CYP2D6 inhibitors elevated the total VEN concentration and the VEN/ODV ratio. Negative correlation between VEN/ODV ratio and genotype sum. 2.6-fold difference between cases with one active <i>CYP2D6</i> allele vs. cases with two active <i>CYP2D6</i> allele ($P < 0.5$). No obvious shift towards <i>N</i> -demethylation pathway was observed. In two PM cases VEN concentration was equal NDV concentration and only minor amounts of ODV were detected.	-	Launiainen <i>et al.</i> [32]
Not reported	Not reported	1	White	3g	CYP2D6 phenotype was not determined. VEN plasma concentration 2.7 mg/l and ODV plasma concentration 1.55 mg/l.	VEN overdose but no cardiovascular toxicity was reported. Patient was discharged 24 h after overdose.	Langford <i>et al.</i> [33]

EM, extensive metabolizer; IM, intermediate metabolizer; NA, not available; NDV, *N*-desmethylvenlafaxine; OCD, obsessive-compulsive disorder; ODV, *O*-desmethylvenlafaxine; PM, poor metabolizer; UM, ultrarapid metabolizer; VEN, venlafaxine.