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Venlafaxine Therapy and *CYP2D6* Genotype

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Introduction

Venlafaxine is an antidepressant used in the treatment of major depressive order, anxiety, and panic disorders. Venlafaxine belongs to the drug class of serotonin and norepinephrine reuptake inhibitors (SNRIs) (1).

The CYP2D6 enzyme metabolizes a quarter of all prescribed drugs, including venlafaxine. This enzyme converts venlafaxine to the active metabolite, O-desmethylvenlafaxine (ODV). Individuals who carry two inactive copies of *CYP2D6* ("poor metabolizers") may have decreased capacity to metabolize venlafaxine, resulting in less active metabolites in their system. In contrast, individuals who carry more than two copies of functional *CYP2D6* alleles ("ultrarapid metabolizers") may have an enhanced capacity to metabolize venlafaxine, resulting in more increased active metabolites in their system.

The FDA states that because the total exposure of venlafaxine and ODV is similar in poor and extensive (normal) metabolizers, there is no need for different venlafaxine dosing regimens for these individuals (1). However, the Dutch Pharmacogenetics Working Group recommends that both poor and intermediate metabolizer genotypes should be treated with an alternative drug, or lower doses of venlafaxine based on clinical response and drug levels. For ultrarapid metabolizer genotypes, they recommend that either the dose of venlafaxine be increased up to 150% of the normal dose, or an alternative drug used (see Table 1 and 2) (2).

Table 1. *CYP2D6* phenotypes and therapeutic recommendations for venlafaxine therapy

Phenotype	Genotype	Recommendations for venlafaxine therapy
Ultrarapid metabolizer	More than two copies of functional alleles	Be alert to decreased venlafaxine and increased O-desmethylvenlafaxine plasma concentration. Titrate dose to a maximum of 150% of the normal dose or select alternative drug (e.g., citalopram, sertraline).
Intermediate metabolizer	One active allele and one inactive allele, or two decreased activity alleles, or one decreased activity allele and one inactive allele	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor O-desmethylvenlafaxine plasma concentration
Poor metabolizer	Two inactive alleles	Insufficient data to allow calculation of dose adjustment. Select alternative drug (e.g., citalopram, sertraline) or adjust dose to clinical response and monitor O-desmethylvenlafaxine plasma concentration.

Table is adapted from Swen J.J., Nijenhuis M., de Boer A., Grandia L. et al. Pharmacogenetics: from bench to byte - an update of guidelines. Clinical pharmacology and therapeutics. 2011;89(5):662–73 (2).

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Table 2. Activity status of *CYP2D6* alleles

Allele type	Alleles
Active	**1, *2, *33, *35*
Decreased activity	**9, *10, *17, *29, *36, *41*
Inactive	**3-*8, *11-*16, *19-*21, *38, *40, *42*

Drug: Venlafaxine

Venlafaxine is an antidepressant that is used for the treatment of a range of psychiatric disorders that include major depressive disorder, generalized anxiety disorder (GAD), social anxiety disorder, and panic disorder (1).

Venlafaxine is thought to exert its antidepressant effect by blocking the transporter reuptake proteins for key neurotransmitters affecting mood, thereby leaving more active neurotransmitters in the synapse. This is known as the "potentiation of neurotransmission."

Venlafaxine belongs to the drug class of serotonin-norepinephrine reuptake inhibitors (SNRIs). However, because venlafaxine also weakly inhibits dopamine reuptake, it is also referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI).

Venlafaxine is metabolized in the liver to its major active metabolite, O-desmethylvenlafaxine (ODV). Venlafaxine and ODV are both potent inhibitors of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake. The formation of ODV is catalyzed by the enzyme CYP2D6. A high ratio of venlafaxine to ODV is a marker of low CYP2D6 activity. Other hepatic enzymes (CYP3A4, CYP2C19, and CYP2C9) metabolize venlafaxine and ODV to minor, less active metabolites (1).

As for all antidepressants, the FDA-approved drug label for venlafaxine includes a black box warning about the risk of suicide: "Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders. Anyone considering the use of venlafaxine or any other antidepressant in a child, adolescent, or young adult must balance this risk with the clinical need." (1)

The toxicity of venlafaxine appears to be higher than for other drugs of the same class. Adverse events include an increase in anxiety, insomnia, and nervousness; the precipitation of mania or hypomania in patients with bipolar disorder; weight loss, reduced appetite, hyponatremia, seizures, cardiac conduction abnormalities, and an increased risk of bleeding events. There is also a risk of discontinuation syndrome, which may occur if therapy is stopped abruptly (a gradual reduction in the dose of venlafaxine is recommended whenever possible) (1, 3).

Gene: *CYP2D6*

The cytochrome P450 superfamily (CYP450) is a large and diverse group of enzymes that form the major system for metabolizing lipids, hormones, toxins, and drugs. The *CYP450* genes are very polymorphic and can result in reduced, absent, or increased enzyme activity.

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants, antipsychotics, analgesics, and beta-blockers. The *CYP2D6* gene is highly polymorphic, with more than 100 star (*) alleles described (4).

*CYP2D6*1* is the wild-type allele and is associated with normal enzyme activity and the "extensive metabolizer" phenotype. The *CYP2D6 *2*, **33*, and **35* alleles are also considered to have near-normal activity. Other alleles include variants that produce a non-functioning enzyme (e.g., **3*, **4*, **5*, and **6*) (5-8) or an enzyme with reduced activity (e.g., **10*, **17*, and **41*) (9-11) (see Table 2). There are large inter-ethnic differences in the

frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **17* more common in Africans, and **10* more common in Asians (12).

Individuals who are intermediate or poor metabolizers carry copies of decreased-function and inactive *CYP2D6* alleles (see Table 1 and 2). In these individuals, the metabolic capacity of CYP2D6 is decreased, which may result in higher levels of venlafaxine and lower levels of ODV.

The FDA-approved drug label for venlafaxine states that although poor metabolizers have increased levels of venlafaxine and decreased levels of ODV compared to individuals with normal CYP2D6 activity, the differences between poor and extensive (normal) metabolizers are not thought to be clinically important because "the sum of venlafaxine and ODV is similar in the two groups and venlafaxine and ODV are pharmacologically approximately equiactive and equipotent." (1) However, the results of some reported studies suggest that side effects are more common in poor metabolizers, and that *CYP2D6* genotyping prior to the initiation of venlafaxine may prevent potential side effects (13, 14). Some of the adverse effects of venlafaxine therapy that have been reported to occur more frequently in poor metabolizers include gastrointestinal side effects, such as vomiting and diarrhea; and cardiovascular side effects, such as hypertension, tachycardia, and prolonged QTc interval (14, 15).

The Dutch Pharmacogenetics Working Group recommendations state that for poor and intermediate metabolizers, there is insufficient data to calculate the dose adjustment for venlafaxine, and an alternative drug should be used (e.g., citalopram, sertraline). Or, the dose of venlafaxine should be adjusted according to the clinical response, and ODV plasma levels should be monitored (2).

Poor metabolizers are commonly found in European Caucasians. The functional *CYP2D6*1* allele is the most common (~70%), and the most common nonfunctional alleles include *CYP2D6*4* and **5*, which largely account for the poor metabolizer phenotype in these populations (16, 17).

In individuals of Asian descent, only about 50% of *CYPD6* alleles are functional, with the reduced function *CYP2D6*10* variant being very common (~40%). As a result, Asians are more likely to be intermediate metabolizers than Caucasians (12). Similarly, in Africans and African Americans, only 50% of *CYPD6* alleles are functional; however, a wider range of variants account for the remaining alleles (18, 19).

Individuals who have multiple functional copies of the *CYP2D6* gene are "ultrarapid metabolizers" (UM). Each allele contributes to the metabolism of venlafaxine to the active metabolite, ODV. Data suggest that the ultrarapid metabolizer phenotype does not have a significant effect on treatment with venlafaxine (efficacy or side effects) but as a precaution, drug levels should be monitored and an increased dose of venlafaxine may be required (13, 14, 20). The Dutch Pharmacogenetics Working Group recommendations state that for ultrarapid metabolizers, there is a need to be alert to decreased venlafaxine and increased ODV concentrations. The dose of venlafaxine should be titrated to a maximum of 150% of the normal dose, or an alternative drug (e.g., citalopram, sertraline) should be considered (2), in patients with normal renal clearance (21).

The ultrarapid metabolizer phenotype is estimated to be present in up to 28% of North Africans, Ethiopians, and Arabs; ~10% in Caucasians; 3% in African Americans, and up to 1% in Hispanics, Chinese, and Japanese (22).

Genetic Testing

Genetic testing is available for many of the more common variant *CYP2D6* alleles. Results are typically reported as a diplotype, such as *CYP2D6 *1/*1* (23). A result for copy number, if available, is also important when interpreting *CYP2D6* results.

If the test results include an interpretation of the patient's predicted metabolizer phenotype, this should be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for nonfunctional, 0.5

for reduced function, and 1 for each copy of a functional allele). The phenotype is defined by the sum of the two scores:

- An extensive (normal) metabolizer phenotype has an activity score of 1 to 2
- An intermediate metabolizer has an activity score of 0.5
- A poor metabolizer has an activity score of 0
- An ultrarapid metabolizer has an activity score greater than 2

Therapeutic Recommendations based on Genotype

This section contains excerpted[1] information on gene-based dosing recommendations. Neither this section nor other parts of this review contain the complete recommendations from the sources.

Statement from the US Food and Drug Administration (FDA): Plasma concentrations of venlafaxine were higher in CYP2D6 poor metabolizers than extensive metabolizers. Because the total exposure (AUC) of venlafaxine and ODV was similar in poor and extensive metabolizer groups, however, there is no need for different venlafaxine dosing regimens for these two groups.

Please review the complete therapeutic recommendations that are located here: (1).

Summary of recommendations from the Pharmacogenetics Working Group of the Royal Dutch Association for the Advancement of Pharmacy (KNMP): For individuals who are poor or intermediate metabolizers, there are insufficient data to calculate a dose adjustment for venlafaxine. Select an alternative drug (e.g., citalopram, sertraline), or adjust the dose of venlafaxine based on the clinical response, and monitor (O-desmethyl)venlafaxine plasma concentration. For individuals who are ultrarapid metabolizers, physicians should be alert to decreased venlafaxine and increased (O-desmethyl)venlafaxine plasma concentration. The dose of venlafaxine should be titrated up to a maximum of 150% of the normal dose or an alternative drug used (e.g., citalopram, sertraline).

Please review the complete therapeutic recommendations that are located here: (2).

Nomenclature

Common allele name	Alternative names	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
*CYP2D6*4*	1846G>A	NM_000106.4:c.506-1G>A	Not applicable - variant occurs in a non-coding region	rs3892097
*CYP2D6*5*	Not applicable - variant results in a whole gene deletion			
*CYP2D6*6*	1707 del T Trp152Gly	NM_000106.4:c.454delT	NP_000097.2:p.Trp152Glyfs	rs5030655
*CYP2D6*10*	100C>T Pro34Ser	NM_000106.4:c.100C>T	NP_000097.2:p.Pro34Ser	rs1065852
*CYP2D6*17*	Includes at least two functional variants*: 1023C>T (Thr107Ile) 2850C>T (Cys296Arg)	NM_000106.4:c.320C>T NM_000106.4:c.886T>C	NP_000097.2:p.Thr107Ile NP_000097.2:p.Cys296Arg	rs28371706 rs16947
*CYP2D6*41*	2988G>A	NM_000106.4:c.985+39 G>	Not applicable – variant occurs in a non-coding region	rs28371725

* In the literature, 1023C>T is also referred to as 1111C>T, and 2850C>T is also referred to 2938C>T.

[1] The FDA labels specific drug formulations. We have substituted the generic names for any drug labels in this excerpt. The FDA may not have labelled all formulations containing the generic drug.

Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS): http://www.hgvs.org/content/guidelines

Nomenclature for Cytochrome P450 enzymes is available from the Human Cytochrome P450 (CYP) Allele Nomenclature Database: http://www.cypalleles.ki.se/

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