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Venlafaxine Therapy and *CYP2D6* Genotype

Laura Dean, MD[1]

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Introduction

Venlafaxine (brand name Effexor) is an antidepressant used in the treatment of major depressive disorder, anxiety, and panic disorders. Venlafaxine belongs to the drug class of serotonin and norepinephrine reuptake inhibitors (SNRIs), as does its major metabolite, desvenlafaxine (brand name Pristiq).

The recommended starting dose for venlafaxine is 75 mg/day, divided into 2 or 3 doses. Depending on tolerability and clinical response, the dose may be increased to 150 mg/day, and if needed, further increased up to 225 mg/day. Only the more severely depressed individuals may respond to higher doses, up to a maximum of 375 mg/day.

Venlafaxine is metabolized into its major active metabolite, O-desmethylvenlafaxine (ODV), primarily by the CYP2D6 enzyme. As such, individuals that have high plasma concentrations of venlafaxine and low plasma concentrations of ODV when taking venlafaxine, indicates they have reduced or absent CYP2D6 activity. This can be caused by concomitant use of medications that inhibit the CYP2D6 enzyme or by germline genetic variation in the *CYP2D6* gene. Individuals who have genetic variants associated with no enzyme activity are called "CYP2D6 poor metabolizers" and account for approximately 7% of Caucasians.

The FDA-approved drug label for venlafaxine does not provide dose adjustments for CYP2D6 poor metabolizers, and states that no dose adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor (Table 1) (1). The label states that although imipramine (an antidepressant that inhibits CYP2D6) was found to partially inhibit venlafaxine metabolism, the total concentration of active compounds (venlafaxine plus ODV) was not affected. In addition, the label cites a clinical study comparing venlafaxine use in CYP2D6 poor metabolizers and normal metabolizers, which found that the total concentration of active compounds (venlafaxine plus ODV) was similar in both metabolizer groups.

However, the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy has published venlafaxine dosing recommendations based on CYP2D6 genotype. For CYP2D6 poor and intermediate metabolizers, DPWG recommends that an alternative drug is used. If an alternative medication is not an option and side effects occur, DPWG recommends a venlafaxine dose reduction based on clinical response and drug levels. For individuals who are CYP2D6 ultrarapid metabolizers (increased CYP2D6 activity), the DPWG recommends increasing the dose of venlafaxine up to 150% of the standard dose, or using an alternative drug if dose adjustment based on therapeutic drug monitoring is not possible (Table 2) (2).

Author Affiliation: 1 NCBI; Email: mgs@ncbi.nlm.nih.gov.

Table 1. FDA Venlafaxine: Drug Interactions and *CYP2D6* (2019)

Phenotype	Recommendations for venlafaxine therapy
CYP2D6 poor metabolizers	In a clinical study involving CYP2D6-poor and -normal metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the 2 metabolizer groups
CYP2D6 inhibitors	No dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor

This FDA table is adapted from (1)

Table 2. DPWG Therapeutic Recommendations for *CYP2D6* and Venlafaxine (2019)

Phenotype	Recommendation
CYP2D6 poor metabolizer	1. Avoid venlafaxine* 2. If it is not possible to avoid venlafaxine and side effects occur: a. reduce the dose b. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine
CYP2D6 intermediate metabolizer	1. Avoid venlafaxine* 2. If it is not possible to avoid venlafaxine and side effects occur: a. reduce the dose b. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine
CYP2D6 ultrarapid metabolizer	1. Be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine 2. if necessary, increase the dose to 150% of the standard dose 3. if dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided*

* Antidepressants that are not metabolized by CYP2D6 –– or to a lesser extent –– include, for example, duloxetine, mirtazapine, citalopram, and sertraline
This DPWG table is adapted from (2)

Drug: Venlafaxine

Venlafaxine is an antidepressant used in the treatment of major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder. An off-label use of venlafaxine is in the management of post-traumatic stress disorder (1, 3).

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). Other drugs with SNRI activity include atomoxetine (used in the treatment of ADHD) and tramadol (an analgesic). However, because venlafaxine also weakly inhibits dopamine reuptake, it is also referred to as a serotonin-norepinephrine-dopamine reuptake inhibitor (SNDRI).

The toxicity of venlafaxine appears to be higher than for other drugs of the same class. Side effects include an increase in anxiety, insomnia, and nervousness; the precipitation of mania or hypomania in individuals with bipolar disorder; as well as 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 venlafaxine therapy is stopped abruptly or if the dose is reduced. Symptoms include agitation, anorexia, anxiety, and confusion. A gradual reduction in the dose of venlafaxine is recommended, whenever possible (4).

Venlafaxine is metabolized in the liver to its major active metabolite, ODV. Venlafaxine and ODV share similar activity, and ODV is also an FDA-licensed antidepressant (desvenlafaxine).

The formation of ODV is catalyzed by the enzyme CYP2D6. Individuals who lack CYP2D6 activity ("CYP2D6 poor metabolizers") have a higher ratio of venlafaxine to ODV compared with normal metabolizers. As such, a venlafaxine:ODV ratio greater than one strongly predicts individuals who are CYP2D6 poor metabolizers (5). Other hepatic enzymes (CYP3A4, CYP2C19, and CYP2C9) also metabolize venlafaxine and ODV to minor, less active metabolites (6).

The FDA-approved drug label for venlafaxine states that although CYP2D6 poor metabolizers have increased levels of venlafaxine and decreased levels of ODV compared with individuals with normal CYP2D6 activity, the differences between poor and normal metabolizers are not thought to be clinically important because the sum of venlafaxine and ODV is similar in the 2 groups.

However, recommendations from the DPWG 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, duloxetine, mirtazapine, sertraline). If an alternative medication is not an option and side effects occur, DPWG recommends a venlafaxine dose reduction based on clinical response, and venlafaxine and ODV plasma level monitoring (7).

The Cytochrome P450 Superfamily

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

Gene: *CYP2D6*

CYP2D6 is responsible for the metabolism of many commonly prescribed drugs, including antidepressants such as venlafaxine, antipsychotics, analgesics, and beta-blockers.

The *CYP2D6* gene on chromosome 22q13.2 is highly polymorphic. Over 100 star (*) alleles have been described and cataloged at the Pharmacogene Variation (PharmVar) Consortium, and each allele is annotated with either normal, decreased or absent enzyme function (when functional status is known) (Table 3). The combination of *CYP2D6* alleles that a person has is used to determine their diplotype (e.g., *CYP2D6* *4/*4), which subsequently is used to assign a phenotype (e.g., CYP2D6 poor metabolizer).

The *CYP2D6*1* is considered the wild-type allele when no variants are detected and is associated with normal enzyme activity and the "normal metabolizer" phenotype. Other *CYP2D6* alleles considered to have normal activity include **2*, **33*, and **35*.

Alleles that encode an enzyme with decreased activity include **10*, **17*, and **41*, and alleles that encode a non-functioning enzyme include **3*, **4*, **5*, and **6*. There are large inter-ethnic differences in the frequency of these alleles, with **3*, **4*, **5*, **6*, and **41* being more common in Caucasians, **10* more common in Asians, and **17* more common in Africans (8).

Table 3. Activity Status of Selected *CYP2D6* Alleles

Effect on enzyme activity	*CYP2D6* alleles
Increased function	**2xN*
Normal function	**1, *2, *33, *35*
Reduced function	**9, *10, *17, *29, *36, *41*

Table 3. continued from previous page.

Effect on enzyme activity	*CYP2D6* alleles
No function	**3, *4, *5, *6, *7, *8, *11, *12, *13, *14, *15, *16, *19, *20, *21, *38, *40, *42*

Note: xN represents the number of *CYP2D6* gene copies.
For a comprehensive list of *CYP2D6* alleles, please see PharmVar.

Table 4. CPIC Assignment of likely *CYP2D6* Phenotype based on Diplotype (2019)

Likely CYP2D6 metabolizer phenotype[b]	Activity score	Genotype[a]	Examples of *CYP2D6* diplotype
Ultrarapid	>2.25	An individual with duplications of functional alleles	*1/*1xN, *1/*2xN, *2/*2xN[c]
Normal	1.25 to 2.25	An individual with 2 normal function alleles or one normal function and one decreased function allele	*1/*1, *1/*2, *1/*9, *1/*41, *2/*2, *1/*10
Intermediate	>0 to <1.25	An individual with one decreased function and one no function allele	*1/*4, *1/*5, *41/*41, *4/*10, *4/*41, *5/*9
Poor	0	An individual with only non functional alleles	*3/*4, *4/*4, *5/*5, *5/*6

[a] Assignment of allele function and citations for allele function can be found on PharmGKB: Gene Reference Materials for *CYP2D6* (*CYP2D6* Allele Definition Table and *CYP2D6* Allele Functionality Table). For a complete list of *CYP2D6* diplotypes and resulting phenotypes, see the *CYP2D6* Genotype to Phenotype Table. Note that genotypes with an activity score of one are classified as NMs in the online *CYP2D6* genotype to phenotype table (9).
[b] See the *CYP2D6* Frequency Table for race-specific allele and phenotype frequencies (9) or see Gaedigk *et al* (10).
[c] Where xN represents the number of *CYP2D6* gene copies. For individuals with *CYP2D6* duplications or multiplications, see supplemental data for additional information on how to translate diplotype into phenotype.
This Clinical Pharmacogenetics Implementation Consortium (CPIC) table is adapted from (11).

CYP2D6 Normal Metabolizers

Most individuals, around 70–80%, are classified as "normal metabolizers" (also referred to as "extensive metabolizers"). They either have 2 normal function alleles (e.g., *1/*1) or one normal and one decreased function allele (e.g., *1/*41). For these individuals, the standard recommended doses of venlafaxine should apply.

Individuals who have one normal function and one no function allele (e.g., *1/*4) or 2 decreased function alleles (e.g., *41/*41) are also categorized as "normal metabolizers" by recent nomenclature guidelines (12), but have also been categorized as "intermediate metabolizers".

CYP2D6 Intermediate and Poor Metabolizers

Individuals who do not have any fully functional alleles are either intermediate metabolizers (one decreased function and one non-functional allele e.g., *4/*41) or poor metabolizers (2 non-functional alleles e.g., *4/*4). In these individuals, the metabolic capacity of CYP2D6 is decreased, resulting in higher levels of venlafaxine and lower levels of ODV.

Approximately 6–10% of European Caucasians and their descendants are poor metabolizers, mainly due to the prevalent non-functional **4* and **5* alleles. Compared with Europeans, individuals of Asian descent are more likely to be intermediate metabolizers because of prevalent decreased function alleles, such as *10. Approximately 30% of Asians and individuals of Asian descent are intermediate metabolizers. Similarly, Africans and African Americans are more likely to be intermediate metabolizers than Europeans because of the prevalence of a wide range of decreased function variants (8, 13-15).

CYP2D6 Ultrarapid Metabolizers

Individuals who have more than 2 normal functional copies of the *CYP2D6* gene are classified as "ultrarapid metabolizers," which accounts for 1–10% of individuals (Table 4). Each allele contributes to the metabolism of venlafaxine to the active metabolite, ODV.

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 (16).

Linking *CYP2D6* Genetic Variation with the Risk of Side Effects and Treatment Response

An individual's CYP2D6 status may influence their risk of side effects from venlafaxine therapy. Individuals who are CYP2D6 poor metabolizers have increased levels of venlafaxine and decreased levels of ODV –– this appears to translate into a higher risk of side effects and a reduced response to therapy (17). Older indivduals may be particularly at risk (18-20).

Side effects reported to occur more frequently in poor metabolizers receiving venlafaxine include gastrointestinal side effects, such as vomiting and diarrhea; and cardiovascular side effects, such as hypertension, tachycardia, and prolonged QTc interval (21, 22).

CYP2D6 genotyping prior to starting venlafaxine therapy would enable personalized dosing, which in combination with therapeutic drug monitoring, could reduce the time taken before an adequate maintenance dose is established, and prevent potential side effects (6, 20, 21, 23-25).

However, evidence for the benefits of routine *CYP2D6* genotyping is mixed. Some studies report that the metabolic changes associated with *CYP2D6* variants do not have a sufficient effect on venlafaxine therapeutic levels, and that *CYP2D6* genotyping would not predict the efficacy of venlafaxine in indivduals with depression (26-30).

Genetic Testing

The NIH's Genetic Testing Registry provides examples of the genetic tests that are currently available for venlafaxine response and for the *CYP2D6* gene.

CYP2D6 is a particularly complex gene that is difficult to genotype because of the large number of variants and the presence of gene deletions, duplications, multiplications, and pseudogenes. The complexity of genetic variation complicates making a correct determination of *CYP2D6* genotype.

Targeted genotyping typically includes up to 30 variant *CYP2D6* alleles (over 100 alleles have been identified so far). Test results are reported as a diplotype, such as *CYP2D6 *1/*1*. However, it is important to note that the number of variants tested can vary among laboratories, which can result in diplotype result discrepancies between testing platforms and laboratories (16).

A result for copy number, if available, is also important when interpreting *CYP2D6* genotyping results. Gene duplications and multiplications are denoted by "xN" e.g., *CYP2D6*1xN with xN representing the number of *CYP2D6* gene copies.

If the test results include an interpretation of the individual's predicted metabolizer phenotype, such as "*CYP2D6* *1/*1, normal metabolizer", this may be confirmed by checking the diplotype and assigning an activity score to each allele (e.g., 0 for no function, 0.5 for decreased function, and 1.0 for each copy of a normal function allele, Table 4).

The *CYP2D6* phenotype is defined by the sum of the 2 activity scores, which is typically in the range of 0 to 3.0:

- An ultrarapid metabolizer has an activity score greater than 2.25
- A normal metabolizer phenotype has an activity score of 1.25 to 2.25
- An intermediate metabolizer has an activity score of >0 to 1.25
- A poor metabolizer has an activity score of 0 (16)

The translation of *CYP2D6* diplotype to phenotype based on the activity score system was recently reported by the CPIC and DPWG (PMID: 31647186) (Table 4).

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.

2019 Statement from the US Food and Drug Administration (FDA)

In vitro and in vivo studies indicate that venlafaxine is metabolized to its active metabolite, ODV, by CYP2D6, the isoenzyme that is responsible for the genetic polymorphism seen in the metabolism of many antidepressants. Therefore, the potential exists for a drug interaction between drugs that inhibit CYP2D6-mediated metabolism and venlafaxine. However, although imipramine partially inhibited the CYP2D6-mediated metabolism of venlafaxine, resulting in higher plasma concentrations of venlafaxine and lower plasma concentrations of ODV, the total concentration of active compounds (venlafaxine plus ODV) was not affected. Additionally, in a clinical study involving CYP2D6-poor and -extensive metabolizers, the total concentration of active compounds (venlafaxine plus ODV), was similar in the two metabolizer groups. Therefore, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.

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

2019 Summary of recommendations from the Dutch Pharmacogenetics Working Group (DPWG) of the Royal Dutch Association for the Advancement of Pharmacy (KNMP)

CYP2D6 Poor Metaboliser

There are indications of an increased risk of side effects and a reduced chance of efficacy.

The gene variation reduces the conversion of venlafaxine to the active metabolite O- desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

1 Avoid venlafaxine

Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

2. If it is not possible to avoid venlafaxine and side effects occur:

[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 labeled all formulations containing the generic drug. Certain terms, genes and genetic variants may be corrected in accordance to nomenclature standards, where necessary. We have given the full name of abbreviations where necessary, other author insertions are shown in square brackets.

a. reduce the dose
b. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine

It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

Furthermore, a reduced effectiveness of venlafaxine has been observed in depression patients with this gene variation.

CYP2D6 Intermediate Metaboliser

There are indications of an increased risk of side effects and a reduced chance of efficacy.

The gene variation reduces the conversion of venlafaxine to the active metabolite O- desmethylvenlafaxine, whilst an association between high O-desmethylvenlafaxine/venlafaxine ratios and response without side effects was found.

It is not possible to offer adequately substantiated advice for dose reduction based on the literature.

1 Avoid venlafaxine

Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

2. if it is not possible to avoid venlafaxine and side effects occur:

a. reduce the dose
b. monitor the effect and side effects or check the plasma concentrations of venlafaxine and O-desmethylvenlafaxine

It is not known whether it is possible to reduce the dose to such an extent that the side effects disappear, while the effectiveness is maintained. In general, it is assumed that the effectiveness is determined by the sum of the plasma concentrations of venlafaxine and O-desmethylvenlafaxine. However, the side effects do not appear to be related to this sum.

CYP2D6 Ultrarapid Metaboliser

It may be difficult to adjust the dose for patients due to altered metabolism between venlafaxine and the active metabolite O-desmethylvenlafaxine. The gene variation increases the conversion of venlafaxine to O-desmethylvenlafaxine and reduces the sum of venlafaxine plus O- desmethylvenlafaxine.

1. be alert to a possible decrease in the sum of the plasma concentrations of venlafaxine and the active metabolite O-desmethylvenlafaxine
2. if necessary, increase the dose to 150% of the standard dose
3. if dose adjustment does not result in efficacy without unacceptable side effects or if dose adjustment based on therapeutic drug monitoring is not possible, then venlafaxine should be avoided

Antidepressants that are not metabolised by CYP2D6 - or to a lesser extent - include, for example, duloxetine, mirtazapine, citalopram and sertraline.

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

Nomenclature

Nomenclature for Selected *CYP2D6* Alleles

Common allele name	Alternative names / major variant	HGVS reference sequence		dbSNP reference identifier for allele location
		Coding	Protein	
CYP2D6*4	1846G>A 4180G>C	NM_000106.5:c.506-1G>A NM_000106.5:c.1457G>C	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	NM_000106.5:c.454delT	NP_000097.3:p.Trp152Glyfs	rs5030655
CYP2D6*10	100C>T Pro34Ser	NM_000106.5:c.100C>T	NP_000097.3:p.Pro34Ser	rs1065852
CYP2D6*17	Includes at least 2 functional variants*: 1023C>T (Thr107Ile) 2850C>T (Arg296Cys)	NM_000106.5:c.320C>T NM_000106.5:c.886C>T	NP_000097.3:p.Thr107Ile NP_000097.3:p.Cys296Arg	rs28371706 rs16947
CYP2D6*41	2988G>A	NM_000106.5:c.985+39G>A	Not applicable––variant occurs in a non-coding region	rs28371725

Note: In the literature, 1023C>T is also referred to as 1111C>T; and 2850C>T is also referred to 2938C>T.
Note: The variant 1846G>A often occurs with both 4180G>C and 100C>T; and the variant 988G>A occurs with 2850C>T. (Cys296Arg).
Pharmacogenetic Allele Nomenclature: International Workgroup Recommendations for Test Result Reporting (31).
Guidelines for the description and nomenclature of gene variations are available from the Human Genome Variation Society (HGVS).
Nomenclature for Cytochrome P450 enzymes is available from Pharmacogene Variation (PharmVar) Consortium.

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