

# Venlafaxine and Desvenlafaxine: Differences and Similarities

[You can watch the video tutorial here](#)

Author: Flavio Guzman, MD

Psychiatrist

Pharmacology Department

University of Mendoza

Argentina

Venlafaxine (Effexor) is an SNRI that is metabolized to O-desmethylvenlafaxine or desvenlafaxine. In 2008 this active metabolite was approved as antidepressant (Pristiq).

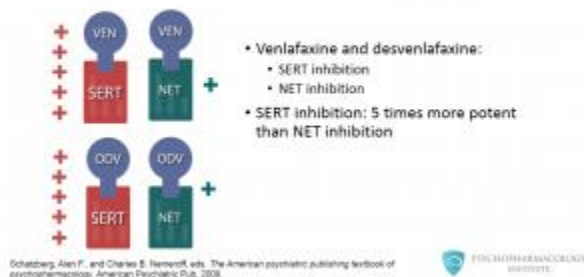
In this multimedia tutorial we discuss what the two drugs have in common and their differences, we also explore mechanisms of action, indications, pharmacokinetics, adverse effects and dosing guidelines.

Important points:

- They are similar in terms of efficacy, pharmacodynamics and side effects profile.
- There are differences in pharmacokinetic aspects and dosing guidelines.

## Mechanism of Action and Pharmacodynamics

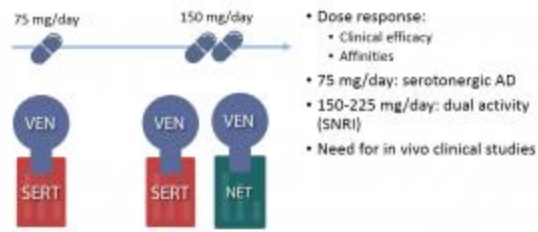
Venlafaxine and Desvenlafaxine – MOA



Both venlafaxine and o- desvenlafaxine inhibit the neuronal reuptake of serotonin. They also inhibit the norepinephrine transporter, but according to in vitro studies the affinity of both drugs is significantly lower for the norepinephrine transporter compared to the SERT.

Venlafaxine is approximately 5 times more potent in vitro as SERT inhibitor versus norepinephrine reuptake inhibitor. This higher serotonergic affinity has been linked to venlafaxine's side effects profile.

## Venlafaxine



Schatzberg, Alan F., and Charles E. Nemeroff, eds. The American psychiatric publishing textbook of psychopharmacology. American Psychiatric Pub, 2008.



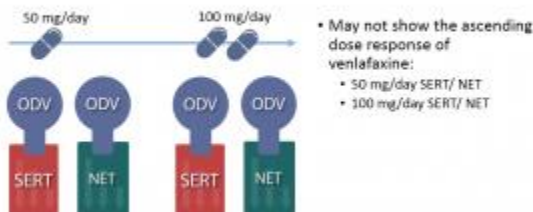
There is evidence from experimental and clinical data suggesting that there is a dose-response relationship in terms of clinical efficacy and pharmacological affinities. At its lower therapeutic dose (75 mg/day), venlafaxine blocks the reuptake only of serotonin. So it can be said that at 75 mgs venlafaxine works as an SSRI.

As the dose increases, so does its noradrenergic effect.

It is believed that at a range of 150-225 mg a day, venlafaxine shows its dual activity as both serotonin and norepinephrine reuptake blocker.

There is one caveat though, this hypothesis cannot be fully tested until a radioactive ligand is developed, so that in vivo clinical studies can be performed. An unrelated example of this type of studies are PET studies that measure D2 receptor occupancy and correlate it with antipsychotic activity.

## Desvenlafaxine



Schatzberg, Alan F., and Charles E. Nemeroff, eds. The American psychiatric publishing textbook of psychopharmacology. American Psychiatric Pub, 2008.



Desvenlafaxine may not show the ascending dose response of venlafaxine. At 50 mg/day the drug inhibits both serotonin and norepinephrine reuptake, affinity doesn't appear to change when the dose is increased to 100 mg/day.

## Indications

### FDA-approved indications

Venlafaxine	Desvenlafaxine
Major depressive disorder	Major depressive disorder
Generalized anxiety disorder	
Social anxiety disorder	
Panic disorder	

Effexor XR (venlafaxine HCl) [package insert], Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc., 2004.  
 Prisdly (desvenlafaxine dextroformin) [package insert], Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc., 2004.



What are the indications for venlafaxine and desvenlafaxine?

Venlafaxine is FDA-approved for major depressive disorder and anxiety disorders, these include: generalized anxiety disorder, social anxiety disorder and panic disorder. Desvenlafaxine is only approved for major depressive disorder.

Are there non approved uses with good level of evidence for venlafaxine? Venlafaxine has also been studied for the treatment of posttraumatic stress disorder.

### Venlafaxine - Non-approved use: PTSD



Beaton L, et al. Venlafaxine extended release in posttraumatic stress disorder: a citalopram- and placebo-controlled study. *Journal of clinical psychopharmacology*. 2006;26(2):209-17.  
 Beaton L, et al. Treatment of post-traumatic stress disorder with venlafaxine extended release: a 6-week randomized-controlled trial. *Archives of general psychiatry*. 2009;63(10):1158-65.



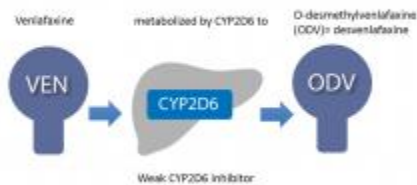
The US VA/Department of Defense clinical practice guidelines recommend venlafaxine as a first line agent for PTSD. The strength of this recommendation is A, this means that the net benefit of the intervention is good and the quality of the evidence is also good.

The guidelines reference two trials of more than 800 participants with non-combat related PTSD. One describes that it is effective and improves resilience and

the other suggests that venlafaxine has similar effectiveness to sertraline.

## Pharmacokinetics

### Venlafaxine/ Desvenlafaxine Pharmacokinetics



Jarvik, P.G., Marder S.R., and Pauluzzi M.N. Principles and Practice of Psychopharmacotherapy, 5th ed. Philadelphia: Lippincott Williams & Wilkins, 2010.



Venlafaxine undergoes metabolism in the liver by the cytochrome P450 2D6 to O-desmethylvenlafaxine, the active metabolite that is commercially available as antidepressant.

Venlafaxine is also a weak inhibitor of CYP2D6, but there are no clinically relevant interactions with most coadministered medications. MAOIs are an exception to

this.

### Venlafaxine/ Desvenlafaxine pharmacokinetics

Metabolizer type	Enzyme activity
Ultrarapid metabolizers	Significantly increased
Extensive metabolizers	Not clinically relevant
Intermediate metabolizers	Not clinically relevant
Poor metabolizers	Significantly decreased

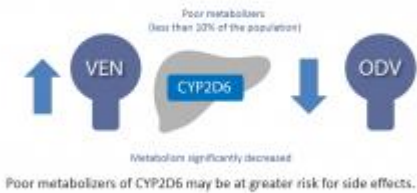
Zanger UM, Raimondo S, Eichelbaum M. Cytochrome P450 2D6: overview and update on pharmacology, genetics, biochemistry. *Muayn Schmiedeberg Arch Pharmacol*. 2004;369(1):23-37.



Let's pause for a minute to discuss a brief concept relevant to venlafaxine pharmacokinetics.

There are several metabolizer types, as you can see in this table, ultrarapid, extensive, intermediate and poor metabolizers. Only poor metabolizers are relevant to our discussion here. Poor metabolizers have significantly decreased CYP450 2D6 activity.

### Venlafaxine/ Desvenlafaxine pharmacokinetics



Mullins DE, O'Keefe DJ, Black JL, Mrazek EA. CYP2D6 genotype variation and venlafaxine dosage. *Mayo Clin Proc.* 2007;82:1565-8.

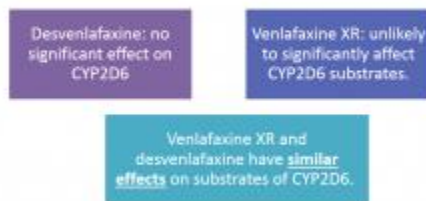


candidates for therapy with desvenlafaxine than the parent drug.

This means that in the case of venlafaxine, this population might have increased concentrations of the parent drug relative to o-desvenlafaxine. Given that the parent drug and o-desvenlafaxine are nearly pharmacologically equipotent, poor metabolizers of CYP2D6 may be at greater risk for side effects.

This group of patients could potentially be better

### Venlafaxine/Desvenlafaxine Pharmacokinetics



Colvard ND. Key Differences Between Venlafaxine XR and Desvenlafaxine: An Analysis of Pharmacokinetic and Clinical Data. *Ment Health Clin.* 2014;4(1):50.



substrates.

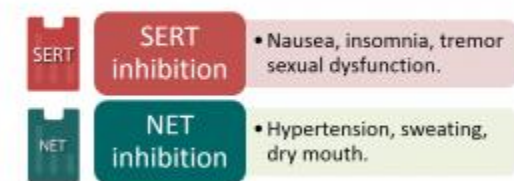
Since desvenlafaxine has no significant effect on CYP2D6 at therapeutic doses, it is promoted as a drug with lower potential for drug-drug interactions with CYP2D6 substrates.

What is interesting here is that venlafaxine is a weak inhibitor of CYP2D6, and the extended release formulation is unlikely to significantly affect CYP2D6

This means that venlafaxine XR and desfenlafaxine have similar effects on substrates of CYP2D6 at recommended doses.

## Adverse Effects – Tolerability

### Venlafaxine Adverse Effects



Thase, M. SNRIs. In Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 9th ed. Philadelphia: LWW, 2005.



In addition to allowing a once-daily dosing, one advantage of the XR formulation is a somewhat lower incidence of nausea during the first weeks of therapy.

Venlafaxine has a tolerability profile linked to increased serotonergic and noradrenergic inhibition. Side effects associated with serotonin reuptake inhibition include: nausea, insomnia, tremor and sexual dysfunction. Some effects associated with norepinephrine reuptake inhibition include hypertension, sweating and dry mouth.

## Venlafaxine Adverse Effects

- One of the antidepressants most commonly associated with discontinuation syndrome.
- XR formulation: somewhat lower incidence of nausea

Thase, M. SWRts, in Kaplan and Sadock's Comprehensive Textbook of Psychiatry, 9th ed. Philadelphia: LWW, 2009.



## Venlafaxine IR and Hypertension



- Dose related effect
- Immediate release studies:

Venlafaxine mg/day	Incidence
<100	3%
100 to <200	6%
200 to <300	7%
>300	13%

Officer (venlafaxine HCl) [package insert]. Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc.;



of 3%, when dosing around 200 to 300 mg/day, the incidence is of 7%. Above 300mg/day the number goes to 13%.

## Venlafaxine XR and Hypertension



- Hypertension can occur with venlafaxine XR
- Caution: patients with preexisting hypertension
- Recommended: blood pressure monitoring, especially when  $\geq 225$ mg/day

Khanani EA, Lawrence O, Malone DA, Jr. Side effects of antidepressants: an overview. Cleveland Clinic journal of medicine. 2006;73(4):431-9, 4-63.



What about the XR formulation? Hypertension can also occur with venlafaxine XR, especially at higher doses.

Prescribers should be cautious when using this medication for patients with preexisting hypertension. The manufacturer recommends blood pressure to be monitored regularly, especially when using venlafaxine XR at doses of 225 mg or more per day.

# Dosing

## Venlafaxine Dosing Guidelines

- Usual dosage range: 75-225 mg/day (can be dosed higher)
  - XR: once daily
  - IR: divided into 2-3 doses
- Dosage forms:
  - Capsule (XR): 37.5 mg, 75 mg, 150 mg
  - Tablet: 37.5 mg, 75 mg, 150 mg, 225 mg
  - Scored tablets: 25 mg, 37.5 mg, 75 mg, 100 mg

Stahl, S.M. The Prescriber's Guide, 4th ed. New York: Cambridge University Press; 2011. (Venlafaxine XR [venlafaxine HCl] [prescribing information], Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc.; 2016.



The usual dosage range recommended by the manufacturer is between 75 to 225 mg/day. Venlafaxine can be dosed higher by experienced prescribers, but always keeping in mind the possibility of drug-induced hypertension.



The extended release formulation allows once daily dosing, while the immediate release formulation needs to be given in two to three doses a day.

The dosage forms include:

- Capsules (XR): 37.5 mg, 75 mg, 150 mg
- Tablets: 37.5 mg, 75 mg, 150 mg, 225 mg
- Scored tablets: 25 mg, 37.5 mg, 75 mg, 100 mg

#### Venlafaxine XR Dosing Guidelines: Depression

- Depression:
  - Starting dose (manufacturer): 75 mg/day
  - Some patients may be better to start at 37mg/day
  - Patients not responding to 75mg/day might benefit from dose increases to 225 mg/day

Effexor XR (venlafaxine HCl) (package insert), Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc.; 2004.



For most patients, the recommended starting dose for venlafaxine XR is 75 mg/day, administered in a single dose.

For some patients, it may be desirable to start at 37.5 mg/day for 4 to 7 days, to allow new patients to adjust to the medication before increasing to 75 mg/day.

Patients not responding to the initial 75 mg/day dose may benefit from dose increases to a maximum of approximately 225 mg/day.

The manufacturer also makes clear that while the maximum recommended dose for moderately depressed outpatients is also 225 mg/day, more severely depressed inpatients in one study of the development program responded to a mean dose of 350 mg/day.

#### Desvenlafaxine – Dosing Guidelines

- Dosage : 50 mg/day
- Dosage forms:
  - XR Tablets: 50 mg, 100 mg
- No evidence that doses greater than 50 mg/day confer any additional benefit.
- 50-400 mg/day effective, but adverse reactions and discontinuations more frequent.

Paxil (desvenlafaxine succinate) (package insert), Philadelphia, Pennsylvania: Wyeth Pharmaceuticals, Inc.; 2005.



Desvenlafaxine dose is of 50 mg/day. Dosage forms include extended release tablets of 50 and 100 mg. This is an important difference with venlafaxine, the development trials showed no evidence that doses greater than 50 mg/day confer any additional benefits

In clinical studies, doses of 50 mg to 400 mg per day were shown to be effective, although no additional benefit was demonstrated at doses greater than 50 mg per day and adverse reactions and discontinuations were more frequent at higher doses.