

Key differences between Venlafaxine XR and Desvenlafaxine: An analysis of pharmacokinetic and clinical data

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ABSTRACT

Venlafaxine XR and its major active metabolite, desvenlafaxine, are serotonin-norepinephrine reuptake inhibitors. Both are FDA-approved for the treatment of major depressive disorder and have essentially the same pharmacologic and pharmacokinetic profiles; however, the recommended dosing is notably different. The FDA approved recommended starting and maintenance dose for desvenlafaxine is 50 mg daily, while venlafaxine XR requires titration from 37.5 mg daily to the maintenance dose of 150 - 225 mg daily. The dose recommendation for desvenlafaxine is based on results from 8-week acute-phase clinical trials, but complete therapeutic response is not always achieved in this short time period. Venlafaxine XR relies on CYP2D6 for conversion to desvenlafaxine while desvenlafaxine has no significant metabolism by CYP2D6 at recommended doses. Both venlafaxine XR and desvenlafaxine have limited clinically significant drug interactions. The most striking difference between the two products is cost.

KEYWORDS

Venlafaxine, desvenlafaxine, pharmacokinetic, metabolite

Venlafaxine extended release (XR) was the first once daily serotonin-norepinephrine reuptake inhibitor (SNRI) approved for the treatment of major depressive disorder (MDD) by the Food and Drug Administration (FDA) in 1997.¹ Approximately ten years later desvenlafaxine (O-desmethylvenlafaxine), the primary major active metabolite of venlafaxine, also joined the market for this indication in the form of desvenlafaxine succinate (Pristiq®).² The FDA also recently approved generic desvenlafaxine fumarate and the free base form of desvenlafaxine as both a generic and brand name (Khedezla ER) products.³⁻⁵ This review will focus on desvenlafaxine succinate as efficacy, pharmacokinetic, and safety data are mostly available for this product.

Venlafaxine and desvenlafaxine are essentially pharmacologically equivalent.^{6,10} Both are potent and selective inhibitors at serotonin and norepinephrine transporters with small differences in binding affinity measured by Ki value (lower Ki value indicates more selective binding).^{2,6-8} The Ki values for serotonin reuptake pumps are 40.2 nM and 82 nM for desvenlafaxine and venlafaxine, respectively.^{7,8} Ki values for norepinephrine reuptake pumps are 558.4 nM and 2480 nM for desvenlafaxine and venlafaxine, respectively.^{7,8} Theoretically, higher binding affinity for desvenlafaxine versus venlafaxine at norepinephrine reuptake pumps could translate into differences in efficacy but this has not been validated in head-to-head clinical trials. Neither agent has significant affinity for

cholinergic, alpha-adrenergic, or histaminergic receptors.^{2,6} No clinically significant differences in adverse effects or tolerability have been identified in clinical trials. A detailed comparison of adverse effects and tolerability among SNRIs was recently published by Alipour.⁹

While there may be subtle variances in receptor binding affinity and adverse effects, more notable differences between the two medications are related to metabolism and FDA approved dosage.^{2,6} Because venlafaxine is primarily metabolized by cytochrome P450 (CYP) 2D6, there is concern that alterations in CYP2D6 activity could negatively impact efficacy and tolerability.⁶ For this reason, it has been speculated that desvenlafaxine may be preferred in patients with drug-drug interactions and genetic polymorphisms which affect CYP2D6.¹¹⁻¹⁷ Furthermore, the fact that desvenlafaxine has the same starting and maintenance dose while venlafaxine XR should be gradually titrated may make desvenlafaxine a more appealing choice for some providers and patients.^{2,6} The clinical impact of these differences has not been fully described. This article will review the data related to differences in metabolism and dosing between venlafaxine XR and desvenlafaxine to describe clinical significance.

Pharmacokinetic Comparison

At least 92% of a single dose of venlafaxine XR is absorbed and subsequently undergoes presystemic hepatic metabolism. It is estimated that 55% of a single

dose is converted to desvenlafaxine via CYP2D6-mediated phase I oxidative metabolism. CYP1A2, CYP3A4, and CYP2C19 are responsible for the formation of other minor inactive oxidative metabolites including N-desmethylvenlafaxine and N,O-didesmethylvenlafaxine.⁶ Unlike venlafaxine, desvenlafaxine is primarily inactivated via phase II glucuronidation with minimal oxidative metabolism via CYP3A4 to N,O-didesmethylvenlafaxine.² Both venlafaxine XR and desvenlafaxine are primarily renally eliminated as varying concentrations of unchanged drug, active, and inactive metabolites.^{2,6} Because venlafaxine XR relies on CYP2D6 for conversion to the major active metabolite, there has been much investigation of the differences in its pharmacokinetic parameters and clinical efficacy among patients with CYP2D6 polymorphisms (polymorphisms in the CYP2D6 gene can result in phenotypes with varying levels of metabolic activity).⁶ Extensive (EM) and intermediate metabolizers (IM) are considered to have 'normal' levels of enzyme activity while ultrarapid (UM) and poor metabolizers (PM) have significantly increased or decreased levels of enzyme activity, respectively.¹⁸ While the majority of the population are EMs, up to 7% of Caucasians are CYP2D6 PMs.¹⁹ Some have concluded that desvenlafaxine may be preferred in this population since it does not require CYP2D6 for clinical activity or clearance unlike many other antidepressants including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants, duloxetine, and venlafaxine.^{11,13,16}

In an attempt to quantify the effect of differences in metabolism between medications, the variances in medication metabolite plasma concentrations among CYP2D6 phenotypes have been measured. Studies evaluating plasma concentrations of venlafaxine and desvenlafaxine following administration of venlafaxine XR have clearly and consistently found the desvenlafaxine/venlafaxine ratio to be significantly lower in PMs when compared to EMs.^{11,13,16} However, no difference in desvenlafaxine serum concentrations was found between PMs versus EMs following administration of desvenlafaxine in these studies. Of note, the sum of venlafaxine and desvenlafaxine did not differ between PM and EM groups receiving venlafaxine XR.^{11,13,16} Considering that venlafaxine and desvenlafaxine are "pharmacologically approximately equiactive and equipotent" and clinical efficacy results from the net contribution of both compounds, one would not expect there to be clinically meaningful differences in efficacy and tolerability between PMs and EMs.⁶

Studies have examined the possibility of decreased

venlafaxine tolerability and efficacy in PMs versus EMs. One retrospective review that included patients who experienced adverse effects or insufficient clinical response to venlafaxine IR or XR found CYP2D6 PMs were significantly more likely to be on lower doses of venlafaxine (n=5; 100% taking 75 mg) versus other phenotypes (n=33; 78.8% taking ≥ 150 mg).¹⁴ Reasons for venlafaxine discontinuation or dose decrease in PMs included increased anxiety, insomnia, decreased appetite, somnolence, and fatigue. This finding may support the theory that CYP2D6 PM phenotype contributes to varied patient treatment response with venlafaxine; however, demographics as well as initial dosing and dosing titrations were not consistent between groups. Prospective randomized trials are needed to confirm this conclusion. Another retrospective review included German patients who experienced adverse effects or insufficient clinical response while taking CYP2D6 dependent antidepressants (i.e., fluoxetine, n=3; paroxetine, n=2; and fluvoxamine, n=1; amitriptyline, n=9; doxepin, n=5; venlafaxine, n=3; maprotiline, n=2; clomipramine, n=1; imipramine, n=1; trimipramine, n=1).¹⁵ There was a significantly higher incidence of CYP2D6 PMs (28%) among those who experienced adverse effects or insufficient clinical response while taking CYP2D6 dependent antidepressants than found in the general population (7%). Unlike venlafaxine, other antidepressants included in this review do not have pharmacologically equivalent active metabolites. Therefore, increased side effects are expected to occur in CYP2D6 PMs as the parent drug serum concentration accumulates. Results of this review cannot be generalized to venlafaxine as statistical significance cannot be determined for the small number patients who experienced side effects on venlafaxine. Only one prospective study has demonstrated a statistically significant increased risk of side effects in PMs versus EMs taking a venlafaxine product.¹² When compared to EMs, CYP2D6 PMs taking venlafaxine IR for depression indications had a higher mean number of side effects (2.3 vs. 0.49; $p < 0.005$) and lower mean serum sodium concentrations (138 vs. 142 mg/dL; $p < 0.05$). There does not appear to be a difference in severe side effects between the groups as the most commonly reported side effects were gastrointestinal side effects, and the difference in serum sodium concentrations does not appear to be clinically significant.¹² No significant differences in efficacy outcomes were found in these studies.^{12,14-15} There is also one pooled analysis of four double blind, placebo-controlled trials (6 – 12 weeks) of patients with major depressive disorder that found

significant differences in depression efficacy outcomes between EMs and PMs taking venlafaxine XR and IR.¹¹ The EMs had significantly greater improvements in change from baseline Hamilton Depression Rating Scale, 17-item (HAM-D₁₇) and Montgomery Asperger Depression Rating Scale (MADRS) scores, HAM-D₁₇ response rate, and MADRS response and remission rates. The HAM-D₁₇ remission rates and incidence of side effects did not differ between the two groups. Despite the inherent limitations of this pooled analysis of clinical trials using varying venlafaxine formulations and protocols, these results suggest that CYP2D6 PMs may respond less favorably to venlafaxine XR therapy than EMs.¹¹ Head to head studies comparing efficacy of desvenlafaxine and venlafaxine XR in PMs are necessary to make definitive recommendations for treatment of this population. Because CYP2D6 PMs account for only 1 – 2% of African Americans; 1% of Asians; and up to 7% of Caucasians, it is not necessary to select desvenlafaxine over venlafaxine XR regularly to avoid intolerance or insufficient response to therapy.¹⁹ Pharmacogenetic testing with the AmpliChip CYP450 may be helpful for some patients who experience intolerance or other difficulties with venlafaxine XR or other antidepressants.¹⁹ Considering it costs approximately \$2,000 yearly for desvenlafaxine and \$150 yearly for generic venlafaxine XR (based on average wholesale price), it actually is less expensive to perform CYP2D6 phenotyping (\$250 - \$500) before initiating antidepressant therapy than to choose desvenlafaxine over venlafaxine for most patients.¹⁹⁻²⁰

Another potential difference between desvenlafaxine and venlafaxine XR is also related to metabolism: the risk for pharmacokinetic drug-drug interactions. Because desvenlafaxine has no significant effect on CYP2D6 at recommended doses, it is promoted as an appealing option to avoid potential drug-drug interactions with CYP2D6 substrates (e.g., many beta blockers, SSRIs, tricyclic antidepressants, opioids). However, venlafaxine XR is also unlikely to significantly affect CYP2D6 substrates. Venlafaxine IR was found to have lower inhibitory potency for CYP2D6 than any SSRI in *in vitro* studies.²² Venlafaxine XR and desvenlafaxine have similar effects on substrates of CYP2D6 at recommended doses. In pharmacokinetic studies, venlafaxine IR 37.5 mg every 12 hours and desvenlafaxine 100 mg increased CYP2D6 substrate desipramine area under the curve (AUC) by 35% and 17% respectively.^{2,6} It is interesting to note that a single dose of desvenlafaxine 400 mg increased desipramine AUC by 90%, so some CYP2D6 substrates with dose related side effects (e.g., tamoxifen, beta-blockers) may require dose reduction when combined

with a higher dose of desvenlafaxine.² In regard to other potential mechanisms for interactions, both venlafaxine and desvenlafaxine are weak inhibitors of CYP3A4 and CYP1A2 and have minimal protein binding (27%, 30% respectively) making both agents unlikely to result in related interactions.^{2,5,23} Combination with strong CYP2D6 inhibitors (i.e., paroxetine, fluoxetine, quinidine, bupropion) may impact venlafaxine XR more than desvenlafaxine, but clinical significance is unknown.^{2,17,21} The combination of venlafaxine XR with a strong CYP2D6 inhibitor should result in decreased desvenlafaxine/venlafaxine ratios just as seen in patients who are CYP2D6 PMs.⁶ Evidence of less favorable venlafaxine efficacy and tolerability with lower desvenlafaxine/venlafaxine ratios found in PMs is limited, and there does not appear to be a difference in serious adverse events when compared to EMs.¹¹⁻¹² It is acceptable to combine venlafaxine XR with CYP2D6 inhibitors, if indicated. There are very few combinations that are likely to occur between venlafaxine XR and strong CYP2D6 inhibitors. SNRIs are not typically combined with SSRIs which leaves bupropion as the most likely interacting inhibitor.

The difference in FDA recommended dosing between venlafaxine XR and desvenlafaxine may make desvenlafaxine more appealing to some providers and patients. Desvenlafaxine is marketed as “an SNRI with a starting dose that is the proven effective dose” while venlafaxine XR requires titration to reach the maximum daily recommended dose of 225 mg.^{6,17} However, comparison of bioavailability between venlafaxine XR and desvenlafaxine make this difference in recommended daily dosing somewhat unexpected. While the absolute bioavailability of venlafaxine XR is 45%, the bioavailability of total active drug is similar between venlafaxine XR (45% venlafaxine + 47% desvenlafaxine) and desvenlafaxine (80% desvenlafaxine).^{2,6} This is illustrated in results from pharmacokinetic studies. Following administration of venlafaxine XR 75 mg to seven EMs, the mean (± SD) maximum plasma concentration (C_{max}) and AUC were 30.1 ng/mL (17.7) and 518 (462) ng/mL for venlafaxine and 94.2 ng/mL (27.4) and 2589 (541) ng/mL for desvenlafaxine. When the same EMs were given desvenlafaxine 50 mg, the C_{max} and AUC of desvenlafaxine were 84.5 ng/mL (15.4) and 2486 ng/mL (415), respectively.¹³ Considering that the pharmacokinetics of venlafaxine XR and desvenlafaxine are linear and dose proportional up to 450 mg and 600 mg per day, respectively, one would expect equivalent doses of venlafaxine XR and desvenlafaxine to deliver similar amounts of total active drug (venlafaxine +

desvenlafaxine) to systemic circulation.^{2,6} Therefore, it may be unexpected to some that the FDA recommended daily target dose of desvenlafaxine is 50 mg since venlafaxine XR has demonstrated safety and efficacy up to 225 mg per day.

Clinical Trial Results

Despite pharmacokinetic similarities, clinical trial results are of primary importance when examining the safe and effective dosing range of desvenlafaxine. During development, Wyeth Pharmaceuticals sought approval for up to desvenlafaxine 200 mg daily, but the FDA selected 50 mg daily as the recommended dose.¹⁰ Even though results from at least one of four 8-week double-blind, randomized, controlled clinical trials (Table 1) show statistically greater reductions in mean HAM-D₁₇ total scores from baseline versus placebo for each desvenlafaxine dose studied (50 mg, 100 mg, 200 mg, 400 mg), the FDA rationalized that doses higher than 50 mg per day resulted in higher rates of side effects and discontinuations without any additional benefit.^{17, 24-27} Based on this rationale, it is unclear why the 100 mg tablet was also approved. Medications only need to achieve statistical separation from placebo in primary outcome (e.g., mean reduction of HAM-D₁₇ score from baseline) to gain FDA-approval for the treatment of MDD, but depression response and remission rates should also be considered to judge a medication's clinically meaningful outcomes. Response and remission rates are inconsistent among doses in these four short-term trials, and it's possible that there are clinically meaningful differences between 50 mg and higher daily dosages.

When desvenlafaxine 50 mg and 100 mg daily were compared to placebo, the 50 mg dose had a remission rate significantly higher than placebo in only one of two studies.^{25, 27} In a study comparing desvenlafaxine 100 mg, 200 mg, and 400 mg daily to placebo, only desvenlafaxine 400 mg daily had a significantly higher remission rate.²⁴ Duration of treatment is key to clarifying the uncertainty in optimal desvenlafaxine dosing. In the first phase of the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) study, patients received flexible-dose citalopram for up to 14 weeks. Of those who achieved response or remission, 56% and 40%, respectively, did so only at or after 8 weeks of treatment.²⁸ Because complete therapeutic response is not always achieved in 8-week acute-phase clinical trials, longer term double-blind, randomized controlled trials at least 14 weeks in duration comparing depression outcomes between desvenlafaxine 50 mg, 100 mg, 200 mg, and 400 mg doses may be needed to definitively determine the optimal treatment dose.

CONCLUSION

Current safety and efficacy data for the treatment of MDD suggest most patients are just as likely to tolerate and respond to venlafaxine XR as desvenlafaxine.^{11-16,24-27,29-30} Limited evidence has shown the exception to this rule could be CYP2D6 PMs who may respond less favorably to venlafaxine XR than EMs.^{11,12} Because less than 10% of the population are PMs, it is more cost efficient to choose venlafaxine XR or perform pharmacogenetic testing than to initiate desvenlafaxine when treating MDD. For this reason, it is not advisable to

Table 1. Efficacy Results for 8-week, randomized, double blind, placebo controlled trials

Study author (year)	Desvenlafaxine study group	Baseline mean HAM-D 17 total score (SD ^a)	Difference from placebo (95% CI) ^b	Response rate ^g	Remission rate ^h
DeMartinis, et al (2007) ²⁴	Placebo (n=118)	23.1 (2.5)	-	35%	19%
	100 mg (n=114)	23.2 (2.5)	-2.9 ^{c,f}	51% ^c	30%
	200 mg (n=116)	22.9 (2.5)	-2.0	45%	28%
	400 mg (n=113)	23.0 (2.2)	-3.1 ^{c,f}	48% ^c	32% ^c
Septien-Velez, et al (2008) ²⁶	Placebo (n=124)	25.3 (3.3)	-	38%	23%
	200 mg (n=121)	24.8 (2.9)	-3.3 ^c (-5.4, -1.2)	60% ^c	37% ^c
	400 mg (n=124)	25.2 (3.2)	-2.8 ^c (-4.9, -0.7)	56% ^c	34%
Liebowitz et al (2008) ²⁷	Placebo	23.0 (3)	-	NA ^d	24%
	50 mg	23.0 (3)	-1.9 ^c (-3.5, -0.3)	NS ^e	34% ^c
	100 mg	23.0 (3)	-1.5	NS ^e	31%
Boyer, et al (2008) ²⁵	Placebo	24.0 (3)	-	50%	29%
	50 mg	24.0 (2)	-2.5 ^c (-4.1, -0.9)	65% ^c	37%
	100 mg	24.0 (3)	-3.0 ^c (-4.7, -1.4)	63% ^c	45% ^c

^aSD=standard deviation; ^b95% CI calculated from mean change in HAM-D 17 score from baseline to 8-weeks (last observation carried forward) and standard error; ^cp-value < 0.05; ^dNA=data not provided; ^eNS=outcome measure did not significantly separate from placebo; ^funable to calculate 95% CI as standard error/standard deviation not provided by reference; ^gresponse=reduction in HAM-D 17 total score ≥ 50% from baseline at 8 weeks; ^hremission=HAM-D 17 total score < 7 at 8 weeks

add desvenlafaxine to a medication formulary. For those who do take desvenlafaxine, longer term clinical trials comparing depression outcomes among desvenlafaxine 50 mg to 400 mg doses are still needed to definitively determine the maximally effective dose and insure optimal treatment response. Finally, prescription medication cost may be the deciding factor for many patients who require lower cost, generic medications in order to be able to consistently afford their prescriptions and maintain optimal adherence.³¹

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