

Desvenlafaxine for depression

Jana Lincoln, MD, and Sheldon H. Preskorn, MD

Compared with other antidepressants, desvenlafaxine might have more predictable effects and a lower risk of drug-drug interactions because of the way it is metabolized. The FDA approved this selective serotonin-norepinephrine reuptake inhibitor (SNRI)—a major active metabolite of venlafaxine—for treating major depressive disorder (MDD, *Table 1*). In clinical trials, desvenlafaxine was more effective than placebo in improving patients' scores on scales of depressive symptoms and overall improvement.¹

Clinical implications

Unlike other SNRIs (venlafaxine and duloxetine), desvenlafaxine does not depend on cytochrome P450 (CYP) 2D6 for biotransformation. As a result plasma concentrations vary less among individual patients, which should result in more predictable efficacy and tolerability. In addition, unlike bupropion, duloxetine, fluoxetine, and paroxetine, desvenlafaxine does not affect the functional activity of CYP 2D6. This translates into a lower risk of drug-drug interactions and more predictable effects on coadministered drugs that are cleared by CYP 2D6.

How it works

Serotonin, norepinephrine, and dopamine in the CNS are involved in mood and neurovegetative functions that are disturbed in patients with MDD. Desvenlafaxine selectively inhibits serotonin and norepinephrine

Table 1

Desvenlafaxine: Fast facts

Brand name: Pristiq
Class: Serotonin-norepinephrine reuptake inhibitor
Indication: Major depressive disorder
Approval date: February 2008
Availability date: May 2008
Manufacturer: Wyeth Pharmaceuticals
Dosing forms: 50- and 100-mg tablets
Recommended dose: 50 to 100 mg/d

New SNRI may have more predictable effects and a lower risk of drug-drug interactions

reuptake pumps, therefore increasing serotonin and norepinephrine concentration in the synaptic cleft.² The drug has weak binding affinity for the dopamine transporter and does not cause substantial changes in extracellular dopamine concentration. Decreased presynaptic serotonin and norepinephrine uptake increases the synaptic concentration of these neurotransmitters. These effects are thought to be responsible for desvenlafaxine's antidepressant efficacy.

Pharmacokinetics

Desvenlafaxine's single-dose pharmacokinetics are linear and dose-proportional over the recommended 50 to 100 mg/d dosing range. The half-life is approximately

Dr. Lincoln is a clinical instructor and Dr. Preskorn is a professor of psychiatry, University of Kansas Medical Center, Wichita. Dr. Preskorn also is the psychopharmacology Section Editor of *CURRENT PSYCHIATRY* and president and CEO of Clinical Research Institute, Wichita.

Clinical Point

To avoid nausea and dizziness consider starting with every-other-day dosing

11 hours. Steady-state plasma concentration is achieved in 4 to 5 days with once-daily dosing.

Food does not affect intestinal absorption. Bioavailability after oral administration is 80%, and time to reach maximum concentration (T_{max}) is 7.5 hours. Plasma protein binding is 30% and is independent of desvenlafaxine concentration.¹

Desvenlafaxine is excreted renally:

- unchanged (45% at 72 hours after administration)
- as desvenlafaxine-glucuronide
- as N-desvenlafaxine-glucuronide.

Desvenlafaxine-glucuronide is the final metabolite of conjugation reaction with glucuronic acid. N-desvenlafaxine-glucuronide is an end product of a 2-step metabolic reaction that starts with oxidation by CYP 3A4 to produce N-desvenlafaxine, which is conjugated with glucuronic acid to create N-desvenlafaxine-glucuronide. As a result of these metabolic and elimination pathways, dosing adjustment is recommended for patients with severe renal impairment or who are taking a CYP 3A4 inhibitor.

Dosing

Desvenlafaxine is available as 50-mg and 100-mg tablets. The recommended dosage is 50 mg/d, and the maximum recommended dosage in patients with hepatic impairment is 100 mg/d.

No dosing adjustment is necessary for patients with moderate renal impairment. The recommended regimen for those with severe renal impairment or end-stage renal disease is 50 mg every other day.

Instruct patients to take desvenlafaxine at approximately the same time each day, with or without food. Tell them not to discontinue the drug abruptly and to immediately report any adverse effects (AEs).

Efficacy

Desvenlafaxine's antidepressant efficacy was established in four 8-week, randomized, double-blind, placebo-controlled, fixed-dose (50 mg to 400 mg once daily) studies in adult

outpatients who met DSM-IV-TR criteria for MDD.^{1,2,4}

In the first study,³ 461 patients received desvenlafaxine, 100 mg, 200 mg, or 400 mg, or placebo. In the second study,⁴ 369 patients received 200 mg or 400 mg or placebo. In 2 additional studies, a total of 930 patients received 50 mg or 100 mg or placebo.¹

All studies used the 17-item Hamilton Rating Scale for Depression (HAM-D17) to measure depressive symptom improvement and the Clinical Global Impressions-Improvement (CGI-I) scale to measure overall improvement. Desvenlafaxine was more effective than placebo in HAM-D17 score improvement in all 4 studies and in CGI-I score improvement in 3 studies.

In studies comparing 50 mg/d with 100 mg/d, doses >50 mg/d provided no additional benefit. Higher starting fixed doses were associated with more frequent AEs and discontinuation.

Gender or age had no effect on treatment outcome. There was no difference in safety in elderly vs younger patients. Data are insufficient to establish a relationship between race and desvenlafaxine responsiveness. Desvenlafaxine's safety and effectiveness in children and adolescents was not evaluated, and the drug is not approved for these patients.

Tolerability and safety

Desvenlafaxine's tolerability is comparable to that of other SNRIs. In premarketing studies, 12% of patients receiving desvenlafaxine (50 mg/d to 400 mg/d) discontinued treatment because of AEs, compared with 3% in the placebo group. The discontinuation rate in patients receiving 100 mg/d was 8.7% compared with 4.1% in patients taking 50 mg/d.

AEs generally occur during the first week of treatment. In the 8-week trials, the most common AEs were nausea and dizziness (Table 2, page 95). In a long-term study (up to 9 months), the most common AE was vomiting. Although the recommended starting dose is 50 mg/d, to avoid AEs consider beginning with every-other-day dosing.

continued on page 95

continued from page 90

Table 2

Desvenlafaxine trials: Rates of adverse effects

Adverse effect	Desvenlafaxine dose		
	50 mg/d	100 mg/d	Placebo
Nausea	22%	26%	10%
Dizziness	13%	10%	5%
Insomnia	9%	12%	6%
Hyperhidrosis	10%	11%	4%
Constipation	9%	9%	4%
Somnolence	4%	9%	4%
Decreased appetite	5%	8%	2%
Erectile dysfunction	3%	6%	1%
Decreased libido	4%	5%	1%
Anxiety	3%	5%	2%

Source: Reference 1

Abruptly discontinuing desvenlafaxine can cause withdrawal symptoms, including dizziness, nausea, headache, irritability, insomnia, diarrhea, anxiety, abnormal dreams, fatigue, and hyperhidrosis. The frequency of withdrawal symptoms is higher with longer treatment duration. Gradually reducing the dose by administering 50 mg of desvenlafaxine less often can reduce withdrawal symptoms.

Clinical issues

All SNRIs and selective serotonin reuptake inhibitors (SSRIs) have a “black-box” warning about the potential for clinical worsening and increased suicidality early in treatment. Closely monitor patients for suicidal ideation/behaviors during the first months of treatment and with dose changes.

When taken in the third trimester of pregnancy, SNRIs and SSRIs can cause serious neonatal complications—including respiratory distress, cyanosis, apnea, and seizures—that may require longer hospitalization, respiratory support, or tube feeding for the infant. Carefully consider risks and benefits of third-trimester antidepressant use.⁵ Desvenlafaxine is excreted in breast milk and may cause AEs in infants who are breast-fed.

In clinical trials, patients taking desvenlafaxine experienced increased cholesterol, triglycerides, and blood pressure. Monitor these parameters closely in patients taking desvenlafaxine, and use the drug with caution in patients with cerebrovascular and cardiovascular disease.

Other concerns in patients taking desvenlafaxine include:

- Antidepressant medications can trigger hypomania or mania in patients with bipolar disorder.
- Patients—particularly those who are elderly or taking diuretics—may develop hyponatremia as a result of syndrome of inappropriate antidiuretic hormone.
- Patients with an increased risk of glaucoma need to be monitored because of the drug’s effect on blood pressure.

Drug interactions. Coadministering desvenlafaxine with serotonergic medications—such as triptans, other antidepressants, and tramadol—can cause serotonin syndrome, a potentially life-threatening condition characterized by mental status changes, autonomic instability, neuromuscular aberrations, and gastrointestinal symptoms. Concomitant use of desvenlafaxine and blood-thinning medications such as warfarin, aspirin, and nonsteroidal anti-inflammatory drugs may

Clinical Point

Desvenlafaxine is excreted in breast milk and may cause AEs in infants who are breast-fed

result in abnormal bleeding. Patients taking a potent CYP 3A4 inhibitor such as ketoconazole may have increased desvenlafaxine concentration.

Contraindications

Do not prescribe desvenlafaxine to patients who are:

- hypersensitive to venlafaxine chloride, desvenlafaxine succinate, or any parts of the desvenlafaxine formulation
- taking a monoamine oxidase inhibitor (MAOI), or have discontinued an MAOI within 14 days.

Patients who stop taking desvenlafaxine should wait 7 days before starting an MAOI.

References

1. Pristiq [package insert]. Philadelphia, PA: Wyeth Pharmaceuticals; 2008.
2. Deecher DC, Beyer CE, Johnston G, et al. Desvenlafaxine succinate: a new serotonin and norepinephrine reuptake inhibitor. *J Pharmacol Exp Ther* 2006;318(2):657-65.
3. DeMartinis NA, Yeung PP, Entsuaeh R, Manley AL. A double-blind, placebo-controlled study of the efficacy and safety of desvenlafaxine succinate in the treatment of major depressive disorder. *J Clin Psychiatry* 2007;68(5):677-88.

Related Resource

• Pristiq (desvenlafaxine) prescribing information. www.wyeth.com/content/showlabeling.asp?id=497.

Drug Brand Names

Bupropion • Wellbutrin	Paroxetine • Prozac
Desvenlafaxine • Pristiq	Tramadol • Ultram
Duloxetine • Cymbalta	Venlafaxine • Effexor
Fluoxetine • Prozac	Warfarin • Coumadin
Ketoconazole • Nizoral	

Disclosures

Dr. Lincoln reports no financial relationship with any company whose products are mentioned in this article or with manufacturers of competing products.

Dr. Preskorn has in the past year received research/grant support from and served as a speaker for Wyeth Pharmaceuticals. Previously, he has received research/grant support from or served as a speaker for or consultant to Abbott Laboratories, AstraZeneca, Aventis, Biovail, Boehringer Ingelheim, Bristol-Myers Squibb, Eisai, Eli Lilly and Company, GlaxoSmithKline, Hoffman LaRoche, Janssen, L.P., Johnson & Johnson, Lundbeck, Merck, Novartis, Organon, Otsuka, Pfizer Inc., Solvay, Somerset, Sumitomo, and Yamanouchi.

4. Septien-Velez L, Pitrosky B, Padmanabhan SK, et al. A randomized, double-blind, placebo-controlled trial of desvenlafaxine succinate in the treatment of major depressive disorder. *Int Clin Psychopharmacol* 2007;22(6):338-47.
5. Lennestål R, Källén B. Delivery outcome in relation to maternal use of some recently introduced antidepressants. *J Clin Psychopharmacol* 2007;27(6):607-13.

Clinical Point

Concomitant use of desvenlafaxine and blood-thinning agents may result in abnormal bleeding

Bottom Line

In 4 clinical trials, desvenlafaxine, 50 mg/d, safely and effectively reduced depressive symptoms. Dosages >50 mg/d showed no evidence of added benefit. The drug's metabolic profile—metabolism independent of CYP 2D6 and substantial renal excretion of unchanged medication—makes desvenlafaxine suitable for patients with liver impairment, in dosages ≤100 mg/d. Patients with severe renal impairment need every-other-day dosing.

Thinking of a job change?



Log on to

MEDopportunities.com

and get started!