DESVENLAFAXINE

**Brands** • Pristiq
*see index for additional brand names*

**Generic?** No

**Class**
- Neuroscience-based Nomenclature: serotonin norepinephrine reuptake inhibitor (SN-RI)
- SNRI (dual serotonin and norepinephrine reuptake inhibitor); often classified as an antidepressant, but it is not just an antidepressant

**Commonly Prescribed for**
*bold for FDA approved*
- Major depressive disorder
- Vasomotor symptoms
- Fibromyalgia
- Generalized anxiety disorder (GAD)
- Social anxiety disorder (social phobia)
- Panic disorder
- Posttraumatic stress disorder (PTSD)
- Premenstrual dysphoric disorder (PMDD)

**How the Drug Works**
- Boosts neurotransmitters serotonin, norepinephrine/noradrenaline, and dopamine
- Blocks serotonin reuptake pump (serotonin transporter), presumably increasing serotonergic neurotransmission
- Blocks norepinephrine reuptake pump (norepinephrine transporter), presumably increasing noradrenergic neurotransmission
- Desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, desvenlafaxine can increase dopamine neurotransmission in this part of the brain

**How Long Until It Works**
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6 or 8 weeks for depression, it may require a dosage increase or it may not work at all
- May continue to work for many years to prevent relapse of depressive symptoms
- Vasomotor symptoms in perimenopausal women with or without depression may improve within 1 week

**If It Works**
- The goal of treatment is complete remission of current symptoms as well as prevention of future relapses
- Treatment most often reduces or even eliminates symptoms, but not a cure since symptoms can recur after medicine stopped
- Continue treatment until all symptoms are gone (remission) or significantly reduced
- Once symptoms are gone, continue treating for 1 year for the first episode of depression
- For second and subsequent episodes of depression, treatment may need to be indefinite

**If It Doesn’t Work**
- Many patients have only a partial response where some symptoms are improved but others persist (especially insomnia, fatigue, and problems concentrating)
- Other patients may be nonresponders, sometimes called treatment-resistant or treatment-refractory
- Some patients who have an initial response may relapse even though they continue treatment, sometimes called “poop-out”
- Consider increasing dose, switching to another agent, or adding an appropriate augmenting agent
- Consider psychotherapy
- Consider evaluation for another diagnosis or for a comorbid condition (e.g., medical illness, substance abuse, etc.)
- Some patients may experience apparent lack of consistent efficacy due to activation of latent or underlying bipolar disorder, and require antidepressant discontinuation and switch to a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Mirtazapine (“California rocket fuel”; a potentially powerful dual serotonin and norepinephrine combination, but observe for activation of bipolar disorder and suicidal ideation)
- Bupropion, reboxetine, nortriptyline, desipramine, maprotiline, atomoxetine (all potentially powerful enhancers of noradrenergic action, but observe for activation of bipolar disorder and suicidal ideation)
• Modafinil, especially for fatigue, sleepiness, and lack of concentration
• Mood stabilizers or atypical antipsychotics for bipolar depression, psychotic depression, or treatment-resistant depression
• Benzodiazepines
• If all else fails for anxiety disorders, consider gabapentin or tiagabine
• Hypnotics or trazodone for insomnia
• Classically, lithium, buspirone, or thyroid hormone

Tests
• Check blood pressure before initiating treatment and regularly during treatment

**SIDE EFFECTS**

**How Drug Causes Side Effects**
• Theoretically due to increases in serotonin and norepinephrine concentrations at receptors in parts of the brain and body other than those that cause therapeutic actions (e.g., unwanted actions of serotonin in sleep centers causing insomnia, unwanted actions of norepinephrine on acetylcholine release causing constipation and dry mouth, etc.)
• Most side effects are immediate but often go away with time

**Notable Side Effects**
• Most side effects increase with higher doses, at least transiently
• Insomnia, sedation, anxiety, dizziness
• Nausea, vomiting, constipation, decreased appetite
• Sexual dysfunction (abnormal ejaculation/ orgasm, impotence)
• Sweating
• SIADH (syndrome of inappropriate antidiuretic hormone secretion)
• Hyponatremia
• Increase in blood pressure

**Life-Threatening or Dangerous Side Effects**
• Rare seizures
• Rare induction of hypomania
• Rare activation of suicidal ideation and behavior (suicidality) (short-term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo beyond age 24)

**Weight Gain**
• Reported but not expected

**Sedation**
• Occurs in significant minority
• May also be activating in some patients

**What to Do About Side Effects**
• Wait
• Wait
• Wait
• Lower the dose
• In a few weeks, switch or add other drugs

**Best Augmenting Agents for Side Effects**
• Often best to try another antidepressant monotherapy prior to resorting to augmentation strategies to treat side effects
• Trazodone or a hypnotic for insomnia
• Bupropion, sildenafil, vardenafil, or tadalafil for sexual dysfunction
• Benzodiazepines for jitteriness and anxiety, especially at initiation of treatment and especially for anxious patients
• Mirtazapine for insomnia, agitation, and gastrointestinal side effects
• Many side effects are dose-dependent (i.e., they increase as dose increases, or they reemerge until tolerance redevelops)
• Many side effects are time-dependent (i.e., they start immediately upon dosing and upon each dose increase, but go away with time)
• Activation and agitation may represent the induction of a bipolar state, especially a mixed dysphoric bipolar II condition sometimes associated with suicidal ideation, and require the addition of lithium, a mood stabilizer or an atypical antipsychotic, and/or discontinuation of desvenlafaxine

**DOSING AND USE**

**Usual Dosage Range**
• Depression: 50 mg once daily
Dosage Forms
- Tablet (extended-release) 50 mg, 100 mg

How to Dose
- Initial dose 50 mg once daily; maximum recommended dose generally 100 mg once daily; doses up to 400 mg once daily have been shown to be effective but higher doses are associated with increased side effects

Dosing Tips
- Desvenlafaxine is the active metabolite 0-desmethylvenlafaxine (ODV) of venlafaxine, and is formed as the result of CYP450 2D6
- More potent at the serotonin transporter (SERT) than at the norepinephrine transporter (NET), but has greater inhibition of NET relative to SERT compared to venlafaxine
- Nonresponders at lower doses may try higher doses to be assured of the benefits of dual SNRI action
- For vasomotor symptoms, current data suggest that a dose of 100 mg/day is effective
- Do not break or chew tablets, as this will alter controlled-release properties
- For some patients with severe problems discontinuing desvenlafaxine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of desvenlafaxine. While maintaining fluoxetine dosing, first slowly taper desvenlafaxine and then taper fluoxetine
- Be sure to differentiate between reemergence of symptoms requiring reinstitution of treatment and withdrawal symptoms
- May dose up to 400 mg/day in patients who do not respond to lower doses, if tolerated

Overdose
- No fatalities have been reported as monotherapy; headache, vomiting, agitation, dizziness, nausea, constipation, diarrhea, dry mouth, paresthesia, tachycardia
- Desvenlafaxine is the active metabolite of venlafaxine; fatal toxicity index data from the UK suggest a higher rate of deaths from overdose with venlafaxine than with SSRIs; it is unknown whether this is related to differences in patients who receive venlafaxine or to potential cardiovascular toxicity of venlafaxine

Long-Term Use
- See doctor regularly to monitor blood pressure

Habit Forming
- No

How to Stop
- Taper to avoid withdrawal effects (dizziness, nausea, diarrhea, sweating, anxiety, irritability)
- Recommended taper schedule is to give a fully daily dose (50 mg) less frequently
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

Pharmacokinetics
- Active metabolite of venlafaxine
- Half-life 9–13 hours
- Minimally metabolized by CYP450 3A4
- Food does not affect absorption

Drug Interactions
- Tramadlo increases the risk of seizures in patients taking an antidepressant
- Can cause a fatal “serotonin syndrome” when combined with MAOIs, so do not use with MAOIs or for at least 14 days after MAOIs are stopped
- Do not start an MAOI for at least 5 half-lives (5 to 7 days for most drugs) after discontinuing desvenlafaxine
- Can rarely cause weakness, hyperreflexia, and incoordination when combined with sumatriptan or possibly other triptans, requiring careful monitoring of patient
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- NSAIDs may impair effectiveness of SSRIs
- Potent inhibitors of CYP450 3A4 may increase plasma levels of desvenlafaxine, but the clinical significance of this is unknown
• Few known adverse drug interactions
• False-positive urine immunoassay screening tests for phencyclidine (PCP) and amphetamine have been reported in patients taking desvenlafaxine, due to a lack of specificity of the screening tests. False-positive test results may be expected for several days following discontinuation of desvenlafaxine

Other Warnings/Precautions
• Use with caution in patients with history of seizure
• Use with caution in patients with heart disease
• Use with caution in patients with bipolar disorder unless treated with concomitant mood-stabilizing agent
• When treating children, carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
• Distribute the brochures provided by the FDA and the drug companies
• Warn patients and their caregivers about the possibility of activating side effects and advise them to report such symptoms immediately
• Monitor patients for activation of suicidal ideation, especially children and adolescents

Do Not Use
• If patient has uncontrolled angle-closure glaucoma
• If patient is taking an MAOI
• If there is a proven allergy to desvenlafaxine or venlafaxine

Hepatic Impairment
• Doses greater than 100 mg/day not recommended

Cardiac Impairment
• Drug should be used with caution
• Hypertension should be controlled prior to initiation of desvenlafaxine and should be monitored regularly during treatment
• Desvenlafaxine has a dose-dependent effect on increasing blood pressure
• Desvenlafaxine is the active metabolite of venlafaxine, which is contraindicated in patients with heart disease in the UK
• Venlafaxine can block cardiac ion channels in vitro and worsens (i.e., reduces) heart rate variability in depression, perhaps due to norepinephrine reuptake inhibition

Elderly
• Some patients may tolerate lower doses better
• Risk of SIADH with SSRIs is higher in the elderly
• Reduction in the risk of suicidality with antidepressants compared to placebo in adults age 65 and older

Children and Adolescents
• Carefully weigh the risks and benefits of pharmacological treatment against the risks and benefits of nontreatment with antidepressants and make sure to document this in the patient’s chart
• Monitor patients face-to-face regularly, particularly during the first several weeks of treatment
• Use with caution, observing for activation of known or unknown bipolar disorder and/or suicidal ideation, and inform parents or guardians of this risk so they can help observe child or adolescent patients

SPECIAL POPULATIONS

Renal Impairment
• For moderate impairment, recommended dose is 50 mg/day
• For severe impairment, recommended dose is 50 mg every other day
• Patients on dialysis should not receive subsequent dose until dialysis is completed

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation
Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001

- Controlled studies have not been conducted in pregnant women
- Not generally recommended for use during pregnancy, especially during first trimester
- Nonetheless, continuous treatment during pregnancy may be necessary and has not been proven to be harmful to the fetus
- Must weigh the risk of treatment (first trimester fetal development, third trimester newborn delivery) to the child against the risk of no treatment (recurrence of depression, maternal health, infant bonding) to the mother and child
- For many patients this may mean continuing treatment during pregnancy
- Exposure to SSRIs late in pregnancy may be associated with increased risk of gestational hypertension and preeclampsia
- Neonates exposed to SSRIs or SNRIs late in the third trimester have developed complications requiring prolonged hospitalization, respiratory support, and tube feeding; reported symptoms are consistent with either a direct toxic effect of SSRIs and SNRIs or, possibly, a drug discontinuation syndrome, and include respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hypertonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying

Breast Feeding
- Some drug is found in mother's breast milk
- Trace amounts may be present in nursing children whose mothers are on desvenlafaxine
- If child becomes irritable or sedated, breast feeding or drug may need to be discontinued
- Immediate postpartum period is a high-risk time for depression, especially in women who have had prior depressive episodes, so drug may need to be re instituted late in the third trimester or shortly after childbirth to prevent a recurrence during the postpartum period
- Must weigh benefits of breast feeding with risks and benefits of antidepressant
treatment versus nontreatment to both the infant and the mother
- For many patients, this may mean continuing treatment during breast feeding

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
- Patients with retarded depression
- Patients with atypical depression
- Patients with depression may have higher remission rates on SNRIs than on SSRIs
- Depressed patients with somatic symptoms, fatigue, and pain
- Depressed patients with vasomotor symptoms
- Patients who do not respond or remit on treatment with SSRIs

Potential Disadvantages
- Patients sensitive to nausea
- Patients with borderline or uncontrolled hypertension
- Patients with cardiac disease

Primary Target Symptoms
- Depressed mood
- Energy, motivation, and interest
- Sleep disturbance
- Physical symptoms
- Pain

Pearls
- Because desvenlafaxine is only minimally metabolized by CYP450 3A4 and is not metabolized at all by CYP450 2D6, as venlafaxine is, it should have more consistent plasma levels than venlafaxine
- In addition, although desvenlafaxine, like venlafaxine, is more potent at the serotonin transporter (SERT) than the norepinephrine transporter (NET), it has relatively greater actions on NET versus SERT than venlafaxine does at comparable doses
- The greater potency for NET may make it a preferable agent for conditions theoretically associated with targeting norepinephrine actions, such as vasomotor symptoms and fibromyalgia
Suggested Reading


• May be particularly helpful for hot flushes in perimenopausal women
• May be effective in patients who fail to respond to SSRIs
• May be used in combination with other antidepressants for treatment-refractory cases
• May be effective in a broad array of anxiety disorders and possibly adult ADHD, although it has not been studied in these conditions
• May be associated with higher depression remission rates than SSRIs
• Because of recent studies from the UK that suggest a higher rate of deaths from overdose with venlafaxine than with SSRIs, and because of its potential to affect heart function, venlafaxine can only be prescribed in the UK by specialist doctors and is contraindicated there in patients with heart disease
• Overdose data are from fatal toxicity index studies, which do not take into account patient characteristics or whether drug use was first- or second-line
• Venlafaxine’s toxicity in overdose is less than that for TCAs