VENLAFAXINE

**Brands**
- Effexor, Effexor XR, Effexor XL, Efectin, Efexor, Trevilor, Venla

**Generic?**
Yes (except XR form)

**Class**
- Serotonin and norepinephrine reuptake inhibitor (SNRI), antidepressant

**Commonly Prescribed for**
(FDA approved in bold)
- Depression
- Generalized anxiety disorder
- Panic disorder
- Social phobia
- Migraine or tension-type headache prophylaxis
- Diabetic neuropathy
- Other painful peripheral neuropathies
- Cancer pain (neuropathic)
- Depression secondary to stroke
- Stress urinary incontinence
- Fibromyalgia
- Binge-eating disorder
- Insomnia
- Post-traumatic stress disorder
- ADHD
- Perimenopausal/ menopausal hot flashes

**How the Drug Works**
- Blocks serotonin and norepinephrine reuptake pumps, increasing their levels within hours, but antidepressant effects take weeks. Effect is more likely related to adaptive changes in serotonin and norepinephrine receptor systems over time
- Weakly blocks dopamine reuptake pump (dopamine transporter)

**How Long Until It Works**
- Migraines – effective in as little as 2 weeks, but can take up to 10 weeks on a stable dose to see full effect
- Tension-type headache prophylaxis – effective in 4–8 weeks
- Neuropathic pain – usually some effect within 4 weeks

**Diabetic neuropathy** – may have significant improvement with high doses within 6 weeks
**Depression** – 2 weeks but up to 2 months for full effect

**If It Works**
- Migraine/tension-type headache – goal is a 50% or greater reduction in headache frequency or severity. Consider tapering or stopping if headaches remit for more than 6 months or if considering pregnancy
- Neuropathic pain – the goal is to reduce pain intensity and symptoms, but usually does not produce remission. Continue to use and monitor for AEs
- Diabetic neuropathy – the goal is to reduce pain intensity and reduce use of analgesics, but usually does not produce remission. Continue to use and maintain strict glycemic control and diabetic management
- Depression – continue to use and monitor for AEs. May continue for 1 yr following first depression episode or indefinitely if >1 episode of depression

**If It Doesn’t Work**
- Increase to highest tolerated dose
- Migraine and tension-type headache: address other issues, such as medication-overuse, other coexisting medical disorders, such as anxiety, and consider changing to another agent or adding a second agent
- Neuropathic pain: either change to another agent or add a second agent

**Best Augmenting Combos for Partial Response or Treatment-Resistance**
- Headache: For some patients, low-dose polytherapy with 2 or more drugs may be better tolerated and more effective than high-dose monotherapy. May use in combination with AEDs, antihypertensives, natural products, and non-medication treatments, such as biofeedback, to improve headache control
- Neuropathic pain: AEDs, such as gabapentin, pregabalin, carbamazepine and capsaicin, mexiletine are agents used for neuropathic pain. Opioids are appropriate for long-term use in some cases but require careful monitoring
Tests
- Check blood pressure at baseline and when increasing dose

ADVERSE EFFECTS (AEs)

How Drug Causes AEs
- By increasing serotonin and norepinephrine on non-therapeutic responsive receptors throughout the body. Most AEs are dose- and time-dependent

Notable AEs
- Constipation, dry mouth, sweating, blurry vision, loss of appetite, nausea, weight loss or gain, hypertension, headache, asthenia, dizziness, tremor, dream disorder, insomnia, somnolence, abnormal ejaculation, impotence, orgasm disorder, sweating, itching, sedation, nervousness, restlessness

Life-Threatening or Dangerous AEs
- Serotonin syndrome
- Rare hepatitis
- Rare activation of mania or suicidal ideation
- Rare worsening of coexisting seizure disorders

Weight Gain
- Not unusual

Sedation
- Not unusual

- May cause insomnia in some patients

What to Do About AEs
- For minor AEs, lower dose, titrate more slowly, or switch to another agent
- For serious AEs, lower dose and consider stopping, taper to avoid withdrawal

Best Augmenting Agents for AEs
- Try magnesium for constipation

DOSING AND USE

Usual Dosage Range
- 37.5–375 mg/day

Dosage Forms
- Tablet: 25 mg, 37.5 mg, 50 mg, 75 mg, 100 mg
- Extended release: 37.5 mg, 75 mg, 150 mg

How to Dose
- Initial dose 37.5–75 mg taken daily. Increase by 75 mg in 1 week. Titrate as tolerated to effective dose, typically 150–375 mg for pain syndromes. Dose once daily as extended release or divided into 2–3 doses as immediate release

Dosing Tips
- Higher doses are typically used for pain. Extended-release formulation allows for once-a-day dosing and may be better tolerated

Overdose
- Signs and symptoms may include cardiac arrhythmias, usually tachycardia, ECG changes (prolonged QTc interval or bundle branch block), sedation, seizures, bowel perforation, serotonin syndrome, fever, rhabdomyolysis, hyponatremia, blood pressure abnormalities, extrapyramidal effects, headache, nervousness, tremor; death can occur

Long-Term Use
- Safe for long-term use with monitoring of blood pressure

Habit Forming
- No

How to Stop
- Taper slowly (no more than 50% reduction every 3–4 days until discontinuation) to avoid withdrawal. Pain often worsens shortly after decreasing dose

Pharmacokinetics
- Metabolized via the CYP2D6 isoenzyme. Venlafaxine is a weak inhibitor of this isoenzyme. O-desmethylvenlafaxine is the only major active metabolite of venlafaxine.
Half-life 5 h venlafaxine and 11 hrs for active metabolite O-desmethylvenlafaxine

**Drug Interactions**

- CYP2D6 inhibitors (paroxetine, fluoxetine, bupropion), cimetidine, and valproic acid and CYP3A4 inhibitors (clarithromycin, ketoconazole, itraconazole) may increase drug concentration
- The release of serotonin by platelets is important for maintaining hemostasis. Combined use of SSRIs or SNRI’s (such as venlafaxine) and NSAIDs, and/or drugs that effect anticoagulation have been associated with an increased risk of bleeding
- CYP2D6 and 1A2 enzyme inducers, including rifampin, nicotine, phenobarbital, can lower levels
- May decrease effects of antihypertensive medications, such as metoprolol
- May decrease clearance and increase effect of antipsychotics (haloperidol, clozapine.)
- May increase the risk of seizure with tramadol
- May cause serotonin syndrome when used within 14 days of MAO inhibitors
- May increase risk of cardiotoxicity and arrhythmia when used with tricyclic antidepressants

**Other Warnings/Precautions**

- May increase risk of seizure
- Patients should be observed closely for clinical worsening, suicidality, and changes in behavior in known or unknown bipolar disorder

**Do Not Use**

- Proven hypersensitivity to drug
- Concurrently with MAOI; allow at least 14 days between discontinuation of an MAOI and initiation of venlafaxine or at least 7–14 days between discontinuation of venlafaxine and initiation of an MAOI
- In patient with uncontrolled narrow angle-closure glaucoma

**Hepatic Impairment**

- Use with caution. Decrease usual dose by 50%

**Cardiac Impairment**

- Use with caution. Dose-dependent effect on blood pressure

**Elderly**

- No adjustments necessary

**Children and Adolescents**

- Safety and efficacy not established. Use with caution. Observe closely for clinical worsening, suicidality, and changes in behavior, in known or unknown bipolar disorder. Parents should be informed and advised of the risks

**Pregnancy**

- Category C. Generally not recommended for the treatment of headaches or neuropathic pain during pregnancy. Neonates exposed to venlafaxine or other SNRIs or SSRIs late in the third trimester have developed complications necessitating extended hospitalizations, respiratory support, and tube feeding. Respiratory distress, cyanosis, apnea, seizures, temperature instability, feeding difficulty, vomiting, hypoglycemia, hypotonia, hyperreflexia, tremor, jitteriness, irritability, and constant crying consistent with a toxic effect of the drug or drug discontinuation syndrome have been reported

**Breast Feeding**

- Some drug is found in breast milk and use while breast feeding is not recommended

**SPECIAL POPULATIONS**

**Renal Impairment**

- Use with caution. Decrease usual dose by 25–50%

**THE ART OF NEUROPHARMACOLOGY**

**Potential Advantages**

- Very effective in the treatment of multiple pain disorders. Effective for treatment of comorbid depression and anxiety in chronic pain. Less sedation than tertiary amine tricyclic antidepressants (TCAs) (e.g., amitriptyline)
Potential Disadvantages

• May cause or worsen hypertension. Usually higher doses are needed for pain disorders than for depression

Primary Target Symptoms

• Reduction in headache frequency, duration and/or intensity
• Reduction in neuropathic pain

Pearls

• Effect on norepinephrine receptors relative to serotonin is greater at higher doses (150 mg or above). This may explain why higher doses are needed in pain disorders than depression and anxiety
• In patients with migraine or tension-type headache, best responders were those on dosages of 150 mg (XR formulation) or more, and safety and efficacy has been reported at those doses
• May treat chronic pain with effects similar to TCAs with no antihistamine, fewer anticholinergic AEs (e.g., sedation, orthostatic hypotension, etc.)
• Efficacy as well as AEs are usually dose-dependent
• XR formulations allows for once-daily dosing, improves tolerability, and reduces certain AEs (e.g., nausea)
• If high blood pressure is not a major concern, may work well with metoprolol in migraine prophylaxis, as venlafaxine lowers the antihypertensive effect of metoprolol
• Venlafaxine can often precipitate mania in patients with bipolar disorder. Use with caution
• For post-stroke depression, may be superior to SSRIs and may even increase survival
• May be useful as an adjunct for patients with pain and coexisting ADHD

Suggested Reading


