VENLAFAXINE

**Therapeutics**

**Brands**
- Effexor
- Effexor XR

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: Serotonin and 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)
- Depression
- 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
- Presumably desensitizes both serotonin 1A receptors and beta adrenergic receptors
- Since dopamine is inactivated by norepinephrine reuptake in frontal cortex, which largely lacks dopamine transporters, venlafaxine can increase dopamine neurotransmission in this part of the brain
- Weakly blocks dopamine reuptake pump (dopamine transporter), and may increase dopamine neurotransmission

**How Long Until It Works**
- Onset of therapeutic actions usually not immediate, but often delayed 2–4 weeks
- If it is not working within 6–8 weeks for depression, it may require a dosage increase or it may not work at all

**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), especially in depression and whenever possible in anxiety disorders
- Once symptoms 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
- Use in anxiety disorders may also 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 a 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 reuptake inhibitor)
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
- Headache, nervousness, insomnia, sedation
- Nausea, diarrhea, decreased appetite
- Sexual dysfunction (abnormal ejaculation/orgasm, impotence)
- Asthenia, sweating
- SIADH (syndrome of inappropriate antidiuretic hormone secretion)
- Hyponatremia
- Dose-dependent increase in blood pressure

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

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
- Possible weight loss, especially short-term

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

Venlafaxine

Venlafaxine (continued)
Venlafaxine has an active metabolite O-desmethylvenlafaxine (ODV), which is formed as the result of CYP450 2D6. Thus, CYP450 2D6 inhibition reduces the formation of ODV, but this is of uncertain clinical significance.

Consider checking plasma levels of ODV and venlafaxine in nonresponders who tolerate high doses, and if plasma levels are low, experts can prudently prescribe doses above 375 mg/day while monitoring closely.

Do not break or chew venlafaxine XR capsules, as this will alter controlled-release properties.

For patients with severe problems discontinuing venlafaxine, dosing may need to be tapered over many months (i.e., reduce dose by 1% every 3 days by crushing tablet and suspending or dissolving in 100 mL of fruit juice, and then disposing of 1 mL while drinking the rest; 3–7 days later, dispose of 2 mL, and so on). This is both a form of very slow biological tapering and a form of behavioral desensitization (not for XR).

For some patients with severe problems discontinuing venlafaxine, it may be useful to add an SSRI with a long half-life, especially fluoxetine, prior to taper of venlafaxine; while maintaining fluoxetine dosing, first slowly taper venlafaxine and then taper fluoxetine.

Be sure to differentiate between reemergence of symptoms requiring reinstitution of treatment and withdrawal symptoms.

Overdose
- Can be lethal; may cause no symptoms; possible symptoms include sedation, convulsions, rapid heartbeat.
- Fatal toxicity index data from the UK suggest a higher rate of deaths from overdose with venlafaxine than with SSRIs.
- 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, especially at doses >225 mg/day.
VENLAFAXINE (continued)

**Habit Forming**
- No

**How to Stop**
- Taper to avoid withdrawal effects (dizziness, nausea, stomach cramps, sweating, tingling, dysesthesias)
- Many patients tolerate 50% dose reduction for 3 days, then another 50% reduction for 3 days, then discontinuation
- If withdrawal symptoms emerge during discontinuation, raise dose to stop symptoms and then restart withdrawal much more slowly

*Withdrawal effects can be more common or more severe with venlafaxine than with some other antidepressants*

**Pharmacokinetics**
- Parent drug has 3–7 hour half-life
- Active metabolite has 9–13 hour half-life
- Food does not affect absorption

**Drug Interactions**
- Tramadol 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 venlafaxine
- Possible increased risk of bleeding, especially when combined with anticoagulants (e.g., warfarin, NSAIDs)
- Concomitant use with cimetidine may reduce clearance of venlafaxine and raise venlafaxine levels
- Could theoretically interfere with the analgesic actions of codeine or possibly with other triptans
- Few known adverse drug interactions

**Other Warnings/Precautions**
- Use with caution in patients with history of seizures
- 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 venlafaxine

**SPECIAL POPULATIONS**

**Renal Impairment**
- Lower dose by 25–50%
- Patients on dialysis should not receive subsequent dose until dialysis is completed

**Hepatic Impairment**
- Lower dose by 50%

**Cardiac Impairment**
- Drug should be used with caution
- Hypertension should be controlled prior to initiation of venlafaxine and should be monitored regularly during treatment
- Venlafaxine has a dose-dependent effect on increasing blood pressure
- Venlafaxine is contraindicated in patients with heart disease in the UK
- Venlafaxine can block cardiac ion channels in vitro
- Venlafaxine 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.
- Not specifically approved, but preliminary data suggest that venlafaxine is effective in children and adolescents with depression, anxiety disorders, and ADHD.

Breast Feeding

- Some drug is found in mother's breast milk.
- Trace amounts may be present in nursing children whose mothers are on venlafaxine.
- 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.

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 (PLLHR 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.
- 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.

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Patients with retarded depression.
- Patients with atypical depression.
- Patients with comorbid anxiety.
- Patients with depression may have higher remission rates on SNRIs than on SSRIs.
- Depressed patients with somatic symptoms, fatigue, and pain.
- 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.
- Anxiety.
Pears

★ May be effective in patients who fail to respond to SSRIs, and may be one of the preferred treatments for treatment-resistant depression

★ May be used in combination with other antidepressants for treatment-refractory cases

★ XR formulation improves tolerability, reduces nausea, and requires only once daily dosing

★ May be effective in a broad array of anxiety disorders

★ May be effective in adult ADHD

★ Not studied in stress urinary incontinence

★ Has greater potency for serotonin reuptake blockade than for norepinephrine reuptake blockade, but this is of unclear clinical significance as a differentiating feature from other SNRIs

★ In vitro binding studies tend to underestimate in vivo potency for reuptake blockade, as they do not factor in the presence of high concentrations of an active metabolite, higher oral mg dosing, or the lower protein binding which can increase functional drug levels at receptor sites

★ Effective dose range is broad (i.e., 75–375 mg in many difficult cases, and up to 600 mg or more in heroic cases)

★ Preliminary studies in neuropathic pain and fibromyalgia suggest potential efficacy

★ Efficacy as well as side effects (especially nausea and increased blood pressure) are dose-dependent

★ Blood pressure increases rare for XR formulation in doses up to 225 mg

★ More withdrawal reactions reported upon discontinuation than for some other antidepressants

★ May be helpful for hot flushes in perimenopausal women

★ 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

Suggested Reading


