SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Venlafaxine

Effexor XR

Dose-dependent SNRI: serotonergic at low doses, noradrenergic higher up, with the worst discontinuation syndrome of the class.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
75-225 mg/day PO (ER)	5 h; active ODV 11 h	CYP2D6 to ODV; 3A4 minor	1-2 wks; 6-8 wks full

⚠ FDA BOXED WARNING

Suicidality and antidepressant drugs: antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies, with no increase beyond age 24 and reduced risk at 65 and older. Monitor closely for clinical worsening and emergent suicidality.

INDICATIONS

- FDA-approved as the extended-release capsule for major depressive disorder, generalized anxiety disorder, social anxiety disorder, and panic disorder.
- The immediate-release tablet is approved for major depressive disorder only, dosed two or three times daily at **75-225 mg/day**.
- Off-label for post-traumatic stress disorder, where it has positive randomized trial data and appears in VA/DoD guidance as an option.
- Off-label for neuropathic pain, fibromyalgia, and diabetic peripheral neuropathy, though duloxetine carries the actual pain indications.
- Off-label for vasomotor symptoms of menopause at **37.5-150 mg/day**, a common choice for breast cancer survivors on tamoxifen.
- Off-label for ADHD and for migraine prophylaxis, both supported only by small trials and generally used after first-line options fail.

DOSING & TITRATION

- Start the extended-release capsule at **37.5 mg** PO daily with food for four to seven days, then increase to **75 mg/day**.
- Titrate by up to 75 mg at intervals of no less than four days; the usual outpatient maximum is **225 mg/day** of the extended-release form.
- Immediate-release tablets are divided two or three times daily, with up to 375 mg/day used only in severely depressed inpatients.
- Reduce the total daily dose by 25 to 50 percent in renal impairment and by about 50 percent in hepatic impairment.
- Available as 37.5, 75, and 150 mg ER capsules, 37.5 to 225 mg ER tablets, and 25 to 100 mg immediate-release tablets.
- Taper over at least four weeks, and often much longer from higher doses, because abrupt withdrawal is severe and sometimes intolerable.

MECHANISM OF ACTION

- Inhibits the serotonin transporter potently at all doses and the norepinephrine transporter progressively as the dose rises above 150 mg/day.
- Below **75 mg/day** it behaves essentially as an SSRI, which is why partial responders often improve when the dose is pushed higher.
- Noradrenergic engagement at higher doses adds energy, focus, and analgesia but also drives sweating, tachycardia, and rising blood pressure.
- Very weak dopamine transporter inhibition emerges only near the top of the dose range and contributes little to clinical effect.
- Free of muscarinic, histaminic, and alpha-1 blockade, so its adverse effects are almost entirely monoaminergic rather than receptor-blocking.

PHARMACOKINETICS

- Well absorbed with extensive first-pass metabolism; food slightly delays but does not reduce absorption of either formulation.
- Venlafaxine has a short **5 hour** half-life and its equipotent active metabolite O-desmethylvenlafaxine about 11 hours.
- That short half-life is why the extended-release form is preferred and why missed doses so reliably provoke withdrawal symptoms.
- CYP2D6 converts venlafaxine to O-desmethylvenlafaxine, so poor metabolizers carry a higher parent-to-metabolite ratio and more side effects.
- Protein binding is low at about 27 percent and roughly 87 percent of a dose is recovered in urine, so renal impairment raises exposure.

ADVERSE EFFECTS

- Nausea affects roughly 30 percent early on, along with headache, insomnia, dry mouth, dizziness, and dose-related sweating.
- Sustained diastolic hypertension is dose-dependent, uncommon below 150 mg/day and reported in about **13 percent** above 300 mg/day.
- Sexual dysfunction is at least as frequent as with SSRIs and includes reduced libido, delayed ejaculation, and anorgasmia.
- Discontinuation syndrome with dizziness, electric-shock sensations, nausea, and irritability begins within a day of a missed dose.
- Overdose is more dangerous than with SSRIs, with seizures, QRS widening, and cardiotoxicity reported at high ingested doses.
- Hyponatremia, mydriasis with angle-closure glaucoma, increased bleeding, and treatment-emergent mania are the other serious concerns.

MONITORING

- Check blood pressure at baseline, two weeks after each dose increase, and at least quarterly once the dose exceeds **150 mg/day**.
- Treat or reduce the dose if sustained diastolic elevation develops, since the hypertension is dose-related and largely reversible.
- Assess suicidality, activation, and agitation weekly for four weeks and after every dose change, most closely in patients under 25.
- Check serum sodium at baseline and within two to four weeks in older adults or diuretic users, and whenever confusion develops.
- Track response with the PHQ-9, GAD-7, or PCL-5 every two to four weeks and use partial response as the trigger for dose escalation.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP2D6 inhibitors such as bupropion, fluoxetine, and paroxetine raise the parent-to-metabolite ratio and worsen tolerability.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, lithium, and St. John's wort; watch for clonus and hyperthermia.
- Additive hypertensive and tachycardic effects with stimulants, and additive bleeding risk with aspirin, NSAIDs, and anticoagulants.
- Not a meaningful CYP inhibitor itself, so venlafaxine rarely raises levels of other drugs the way paroxetine or fluoxetine do.

SPECIAL POPULATIONS

- Cohort data in pregnancy show no clear teratogenic signal, but third-trimester exposure carries neonatal adaptation and pulmonary hypertension risk.
- Relative infant dose in breast milk is about 6 to 9 percent, higher than sertraline, so monitor the infant if breastfeeding continues.
- Not approved in pediatrics, and pediatric depression trials showed increased hostility and suicidality without clear efficacy.
- In older adults start at **37.5 mg/day** and monitor blood pressure and sodium closely, since both risks increase with age.
- Reduce the dose by 25 to 50 percent when creatinine clearance is under 30 mL/min and by half in moderate to severe hepatic impairment.

PRESCRIBING PEARLS

- Below 75 mg/day it is effectively an SSRI; noradrenergic effects need doses above 150 mg/day.
- Check blood pressure at every dose step above 150 mg/day, since hypertension is dose-related.
- Never stop abruptly. Cross-taper to fluoxetine if withdrawal makes a direct taper impossible.

References

Cipriani, A., Furukawa, T. A., Salanti, G., Chaimani, A., Atkinson, L. Z., Ogawa, Y., Leucht, S., Ruhe, H. G., Turner, E. H., Higgins, J. P. T., Egger, M., Takeshima, N., Hayasaka, Y., Imai, H., Shinohara, K., Tajika, A., Ioannidis, J. P. A., & Geddes, J. R. (2018). Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: A systematic review and network meta-analysis. *The Lancet*, *391*(10128), 1357-1366. https://doi.org/10.1016/S0140-6736(17)32802-7

Furukawa, T. A., Cipriani, A., Cowen, P. J., Leucht, S., Egger, M., & Salanti, G. (2019). Optimal dose of selective serotonin reuptake inhibitors, venlafaxine, and mirtazapine in major depression: A systematic review and dose-response meta-analysis. *The Lancet Psychiatry*, *6*(7), 601-609. https://doi.org/10.1016/S2215-0366(19)30217-2

Kennedy, S. H., Lam, R. W., McIntyre, R. S., Tourjman, S. V., Bhat, V., Blier, P., Hasnain, M., Jollant, F., Levitt, A. J., MacQueen, G. M., McInerney, S. J., McIntosh, D., Milev, R. V., Muller, D. J., Parikh, S. V., Pearson, N. L., Ravindran, A. V., & Uher, R. (2016). Canadian Network for Mood and Anxiety Treatments (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological treatments. *The Canadian Journal of Psychiatry*, *61*(9), 540-560. https://doi.org/10.1177/0706743716659417

National Library of Medicine. (2024). *Venlafaxine*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a694020.html

Stahl, S. M. (2021). *Stahl's essential psychopharmacology: Neuroscientific basis and practical applications* (5th ed.). Cambridge University Press.

Thase, M. E., Entsuah, A. R., & Rudolph, R. L. (2001). Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. *British Journal of Psychiatry*, *178*(3), 234-241. https://doi.org/10.1192/bjp.178.3.234

U.S. Department of Veterans Affairs & U.S. Department of Defense. (2022). *VA/DoD clinical practice guideline for the management of major depressive disorder*. https://www.healthquality.va.gov/guidelines/MH/mdd/

Wyeth Pharmaceuticals. (2024). *Effexor XR (venlafaxine hydrochloride) extended-release capsules [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

NOTE

References follow APA 7th edition style. Dosing, boxed warnings, and interaction data change; confirm every clinical decision against the current FDA prescribing information (DailyMed) and your institution's formulary. This sheet is an educational quick reference and does not replace the full label or clinical judgment.