SEROTONIN-NOREPINEPHRINE REUPTAKE INHIBITOR

Duloxetine

Cymbalta, Drizalma Sprinkle, Irenka

The SNRI of choice when depression or anxiety coexists with chronic pain, carrying real hepatotoxicity and discontinuation liabilities.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
40-60 mg/day PO	12 h	CYP1A2, 2D6; mod 2D6 inhibitor	1-2 wks mood; 1-4 wks pain

⚠ FDA BOXED WARNING

Suicidal thoughts and behaviors: antidepressants increased the risk in children, adolescents, and young adults in short-term studies, with no increase after age 24 and reduced risk at 65 and older. In patients of all ages started on antidepressants, monitor closely for clinical worsening and emergent suicidality.

INDICATIONS

- FDA-approved for major depressive disorder in adults at **40-60 mg/day**, with no added antidepressant benefit demonstrated above 60 mg/day.
- FDA-approved for generalized anxiety disorder in adults and in pediatric patients aged 7 years and older, dosed at 30 to 120 mg/day.
- FDA-approved for diabetic peripheral neuropathic pain in adults at **60 mg once daily**, the dose at which the pivotal trials were run.
- FDA-approved for fibromyalgia in adults and in adolescents aged 13 to 17, and for chronic musculoskeletal pain including osteoarthritis and low back pain.
- Off-label for stress urinary incontinence, an approved indication in Europe but never granted in the United States.
- Off-label for chemotherapy-induced peripheral neuropathy, where it has the strongest randomized evidence of any pharmacologic option.

DOSING & TITRATION

- For depression start **30 mg** PO daily for one week to limit nausea, then increase to the usual target of **60 mg once daily**.
- Generalized anxiety may be started at 30 or 60 mg daily; the labeled maximum is **120 mg/day**, though benefit above 60 mg is limited.
- For neuropathic pain, fibromyalgia, and chronic musculoskeletal pain the target is 60 mg once daily, with no added benefit at 120 mg/day.
- Pediatric generalized anxiety starts at **30 mg** once daily for two weeks, then 60 mg daily, with a range of 30 to 120 mg/day.
- Not recommended when creatinine clearance is under 30 mL/min or in any hepatic insufficiency or chronic liver disease.
- Taper over at least two weeks, using 20 or 30 mg steps, because abrupt discontinuation causes dizziness and paresthesia in many patients.

MECHANISM OF ACTION

- Balanced inhibitor of the serotonin and norepinephrine transporters, with meaningful noradrenergic activity at standard clinical doses.
- Descending noradrenergic and serotonergic pathways from the brainstem to the dorsal horn are the substrate for its analgesic effect.
- That descending inhibition explains why pain responds at doses comparable to those used for mood rather than at higher doses.
- Weak dopamine transporter inhibition contributes little, and there is no clinically relevant muscarinic, histaminic, or adrenergic blockade.
- Noradrenergic tone drives its characteristic effects on blood pressure, sweating, urinary hesitancy, and dry mouth.

PHARMACOKINETICS

- Delivered as enteric-coated pellets because the drug degrades in gastric acid, so capsules must not be crushed or chewed.
- Half-life is about **12 hours**, and although dosed once daily, that short half-life underlies its frequent discontinuation symptoms.
- Metabolized by both CYP1A2 and CYP2D6 into inactive metabolites, with less than 1 percent excreted unchanged in urine.
- It is a moderate CYP2D6 inhibitor, so it raises levels of tricyclics, metoprolol, atomoxetine, and other 2D6 substrates.
- Exposure rises roughly fivefold in end-stage renal disease and about threefold in cirrhosis, which underlies both use restrictions.

ADVERSE EFFECTS

- Nausea affects roughly 25 percent of patients and is worst in the first week, which is the reason for the 30 mg lead-in dose.
- Dry mouth, constipation, somnolence, fatigue, decreased appetite, and hyperhidrosis are common and largely noradrenergically driven.
- Hepatotoxicity ranging from transaminase elevation to rare hepatic failure led to the warning against use in liver disease or heavy alcohol use.
- Blood pressure rises modestly and dose-dependently; sustained hypertension is less frequent than with venlafaxine but still requires monitoring.
- Discontinuation syndrome is common and prominent, with dizziness, nausea, headache, paresthesia, and irritability within days of stopping.
- Sexual dysfunction, hyponatremia, urinary hesitancy, mydriasis, and increased bleeding risk round out the prescribing-relevant effects.

MONITORING

- Obtain baseline liver enzymes in anyone with alcohol use, hepatitis, or fatty liver, and recheck if abdominal pain or jaundice develops.
- Check blood pressure at baseline and periodically, particularly during dose escalation above 60 mg/day.
- Estimate creatinine clearance before starting, since duloxetine is not recommended below 30 mL/min.
- Assess suicidality, activation, and agitation weekly for the first four weeks and after each dose change, especially under age 25.
- Track pain with a numeric rating scale alongside PHQ-9 or GAD-7, since mood and pain responses do not always move together.

INTERACTIONS & CAUTIONS

- Contraindicated with MAOIs and within **14 days** of stopping one, and with linezolid or intravenous methylene blue.
- Strong CYP1A2 inhibitors, especially fluvoxamine and ciprofloxacin, can raise duloxetine exposure severalfold and should be avoided.
- Moderate CYP2D6 inhibition raises levels of tricyclics, metoprolol, atomoxetine, risperidone, and thioridazine, which should be avoided outright.
- Additive serotonin syndrome risk with triptans, tramadol, fentanyl, lithium, and St. John's wort, and additive bleeding risk with NSAIDs.
- Combined use with substantial alcohol intake is discouraged because of the added hepatotoxic risk.

SPECIAL POPULATIONS

- Pregnancy cohort data show no clear teratogenic signal, though late exposure carries neonatal adaptation and postpartum hemorrhage concerns.
- Relative infant dose in breast milk is under 1 percent, so duloxetine is generally considered acceptable during lactation if needed.
- Approved from age 7 for generalized anxiety and from age 13 for fibromyalgia, making it one of the few SNRIs with pediatric labeling.
- In older adults start at **20-30 mg/day** and watch for hyponatremia, falls, urinary retention, and blood pressure elevation.
- Avoid entirely in severe renal impairment and in any hepatic impairment, where exposure rises three to five times over normal.

PRESCRIBING PEARLS

- Best choice when depression rides with neuropathic pain or fibromyalgia; 60 mg/day covers both.
- Avoid in liver disease or heavy alcohol use; hepatotoxicity is the label warning that changes practice.
- Do not use below a creatinine clearance of 30 mL/min, and never crush the enteric-coated pellets.

Verify against the current FDA label and your formulary before prescribing. Educational reference only.

References

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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.