GABAPENTINOID | C-V

Pregabalin

Lyrica, Lyrica CR

Alpha-2-delta calcium channel ligand for neuropathic pain, fibromyalgia and seizures, widely used off-label as a rapid-onset anxiolytic.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
150-600 mg/day PO divided	About 6.3 h	Negligible; renal unchanged	Anxiolysis within about 1 wk

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved for neuropathic pain associated with diabetic peripheral neuropathy, for postherpetic neuralgia and for neuropathic pain after spinal cord injury.
- FDA-approved for management of fibromyalgia in adults, where it was the first agent to carry that specific indication.
- FDA-approved as adjunctive therapy for partial-onset seizures in patients aged **1 month and older**, dosed by weight in children.
- The controlled-release formulation covers diabetic neuropathy and postherpetic neuralgia once daily but is not approved for fibromyalgia.
- Off-label for generalized anxiety disorder, an indication approved in Europe, with effect sizes comparable to SSRIs and onset within a week.
- Off-label use in alcohol withdrawal, restless legs and social anxiety is common but is tempered by real misuse and diversion potential.

DOSING & TITRATION

- Diabetic peripheral neuropathy: start **50 mg** three times daily and increase to 300 mg/day within one week; the maximum for this indication is 300 mg/day.
- Postherpetic neuralgia: start **75 mg** twice daily, move to 300 mg/day within a week, and increase to a maximum of **600 mg/day** if needed.
- Fibromyalgia: start **75 mg** twice daily, increase to 150 mg twice daily within a week, with a maximum of **450 mg/day** in divided doses.
- Adjunctive partial-onset seizures in adults: **150 mg/day** divided two or three times daily, titrated to a maximum of 600 mg/day.
- Reduce by roughly half at creatinine clearance 30-60 mL/min, to a quarter at 15-30, and further below 15, with a supplemental dose after dialysis.
- Taper over at least **1 week** when stopping; abrupt withdrawal causes insomnia, nausea, headache, diarrhea and seizures in epilepsy patients.

MECHANISM OF ACTION

- Binds the alpha-2-delta auxiliary subunit of voltage-gated calcium channels, reducing calcium influx into hyperexcited presynaptic terminals.
- That reduction dampens release of glutamate, norepinephrine and substance P, quieting central sensitization in neuropathic pain states.
- Despite the name it has no direct action at GABA receptors, is not converted to GABA and does not alter GABA reuptake.
- Binding affinity is higher and absorption far more predictable than gabapentin, giving a linear and more reliable dose-response relationship.
- Rapid anxiolysis and dose-dependent euphoria explain both its off-label popularity and its schedule C-V misuse liability.

PHARMACOKINETICS

- Oral bioavailability exceeds **90%** and is dose-independent, unlike gabapentin whose saturable transporter caps absorption at higher doses.
- Elimination half-life is about **6.3 h**, supporting two or three daily doses, or once-daily controlled release after the evening meal.
- Metabolism is negligible: more than **90%** of a dose is excreted unchanged in the urine, so renal function dictates every dose decision.
- It is not protein bound, does not inhibit or induce CYP enzymes, and therefore has essentially no pharmacokinetic drug interactions.
- Hemodialysis removes roughly half of circulating drug in 4 h, so a supplemental dose is required after each session.

ADVERSE EFFECTS

- Dizziness in up to **45%** and somnolence in up to **28%** are dose-related, appear early and are the commonest reasons for discontinuation.
- Peripheral edema affects about **16%** and weight gain of 7% or more occurs in a similar proportion, both worse with thiazolidinediones.
- Blurred vision, dry mouth, ataxia, euphoria and difficulty with attention or word finding occur and matter in older or working patients.
- Respiratory depression can occur with opioids, benzodiazepines or in respiratory disease, a risk the FDA formally warned about in 2019.
- Angioedema, hypersensitivity reactions, thrombocytopenia and rare rhabdomyolysis are uncommon but require prompt discontinuation.
- Suicidal ideation carries the antiepileptic class warning at roughly one additional case per 500 treated, and misuse or dependence does occur.

MONITORING

- Creatinine clearance at baseline and periodically, because dosing is determined almost entirely by renal elimination.
- Weight and lower-extremity edema at each visit, particularly in heart failure or with concurrent thiazolidinedione therapy.
- Sedation, gait and fall risk in older adults, ideally with a formal gait assessment after any dose increase.
- Mood and suicidal ideation, and creatine kinase whenever unexplained muscle pain, tenderness or weakness appears.
- Prescription drug monitoring program review and a misuse assessment when the patient also uses opioids or has a substance use history.

INTERACTIONS & CAUTIONS

- Opioids and other CNS depressants produce additive sedation and respiratory depression, a combination implicated in many overdose deaths.
- Alcohol, benzodiazepines and sedating antihistamines compound cognitive and psychomotor impairment in a dose-dependent way.
- Thiazolidinediones such as pioglitazone add to fluid retention and weight gain and may precipitate heart failure decompensation.
- ACE inhibitors combined with pregabalin appear to raise the risk of angioedema above either agent alone.
- There are no cytochrome P450 or protein-binding interactions, so no adjustment is needed for other psychotropics.

SPECIAL POPULATIONS

- Pregnancy: registry data raise the possibility of a small increase in major congenital malformations, so reserve use for clear indications.
- Lactation: pregabalin is excreted into human milk and breastfeeding during treatment is generally not recommended.
- Pediatric: approved as adjunctive seizure therapy from **1 month** of age with weight-based dosing, generally 2.5-14 mg/kg/day.
- Geriatric: reduce the dose for renal decline and weigh sedation, edema and fall risk; Beers criteria caution against pairing it with opioids.
- Renal impairment governs dosing at every level and requires a supplemental dose after each hemodialysis session; no hepatic adjustment is needed.

PRESCRIBING PEARLS

- Dose it by creatinine clearance; over **90%** leaves the body unchanged in urine.
- Adding an opioid raises overdose death risk, the subject of a 2019 FDA warning.
- It is anxiolytic within a week off-label, but it is C-V and genuinely misused.

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.