GABAPENTINOID

Gabapentin

Neurontin, Gralise, Horizant (gabapentin enacarbil)

Renally cleared calcium channel alpha-2-delta ligand used widely off-label for anxiety, alcohol use disorder, and sleep as well as neuropathic pain.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
900-3600 mg/day PO divided	5-7 h; up to 52 h if anuric	None; renal excretion	Days for pain and anxiety

No FDA boxed warning on the current US label.

INDICATIONS

- FDA-approved as adjunctive therapy for partial-onset seizures in adults and in children aged 3 years and older.
- FDA-approved for postherpetic neuralgia in adults, with the once-daily gastroretentive formulation labeled for the same indication.
- Gabapentin enacarbil is FDA-approved for moderate to severe primary restless legs syndrome and for postherpetic neuralgia.
- Off-label use for alcohol use disorder, where randomized trials show reduced heavy drinking, particularly with withdrawal symptoms.
- Off-label use for generalized and social anxiety, insomnia, hot flashes, and diabetic neuropathy, none of which are labeled indications.
- Off-label use in bipolar disorder is not supported, since controlled trials found gabapentin no better than placebo.

DOSING & TITRATION

- For seizures and neuropathic pain, start **300 mg** on day 1, **300 mg** twice daily on day 2, and 300 mg three times daily on day 3.
- Titrate to a usual effective range of **900-1800 mg/day** in three divided doses, with a labeled maximum of **3600 mg/day**.
- Off-label anxiety or alcohol use disorder dosing typically ranges from **900-1800 mg/day** divided three times daily.
- Adjust for renal function: give 400 to 1400 mg daily at a creatinine clearance of 30 to 59 mL/min and 200 to 700 mg daily at 15 to 29.
- At a creatinine clearance below 15 mL/min give 100 to 300 mg once daily, plus a supplemental dose after each hemodialysis session.
- Do not leave more than 12 hours between doses, and taper over at least 1 week when stopping to avoid withdrawal and seizure risk.

MECHANISM OF ACTION

- Binds the alpha-2-delta auxiliary subunit of voltage-gated calcium channels, reducing channel trafficking to the presynaptic membrane.
- Reduced calcium influx lowers release of glutamate, substance P, and norepinephrine from hyperexcitable presynaptic terminals.
- Despite its name it does not bind GABA-A or GABA-B receptors and is not converted to GABA in the central nervous system.
- Effects on the descending noradrenergic pain pathway contribute to analgesia in neuropathic pain states.
- Anxiolytic and sleep effects likely follow from the same reduction in excitatory neurotransmitter release rather than from GABA mimicry.

PHARMACOKINETICS

- Absorption occurs by a saturable L-amino acid transporter, so bioavailability falls from about 60 percent at 900 mg to 33 percent at 3600 mg.
- Because absorption is saturable, dividing the total dose across three administrations gives more exposure than one large dose.
- Gabapentin is not metabolized and does not induce or inhibit hepatic enzymes, so pharmacokinetic drug interactions are minimal.
- It is excreted unchanged by the kidneys with a half-life of 5 to 7 hours, which lengthens to 50 hours or more in anuric patients.
- Gabapentin enacarbil is a prodrug absorbed by high-capacity transporters, giving more predictable exposure and once-daily dosing.

ADVERSE EFFECTS

- Somnolence affects roughly 20 percent and dizziness roughly 17 percent, both of which are dose-related and worst during titration.
- Ataxia, tremor, nystagmus, and blurred vision are common at higher doses and increase fall risk in older adults.
- Peripheral edema and weight gain occur in a substantial minority and are frequent reasons for discontinuation in chronic use.
- Respiratory depression can occur when gabapentin is combined with opioids or used in patients with COPD or other respiratory compromise.
- Misuse for euphoria and for potentiating opioid effects is well documented, and withdrawal resembles that of sedative-hypnotics.
- Rare serious reactions include drug reaction with eosinophilia and systemic symptoms and anaphylaxis with angioedema.

MONITORING

- Assess renal function at baseline and periodically, since dose requirements track directly with creatinine clearance.
- Screen for sedation, gait instability, and falls at each visit, especially in older adults and those on other CNS depressants.
- Ask specifically about opioid, benzodiazepine, and alcohol use, and about escalating self-directed dose increases suggesting misuse.
- Check the state prescription drug monitoring program where gabapentin is scheduled or monitored, and document the indication.
- Watch for peripheral edema and weight change, and reassess the need for continued therapy at regular intervals.

INTERACTIONS & CAUTIONS

- Concurrent opioids raise gabapentin exposure and markedly increase the risk of sedation, respiratory depression, and overdose death.
- Additive central nervous system depression with benzodiazepines, alcohol, sedating antihistamines, and muscle relaxants.
- Aluminum and magnesium antacids reduce gabapentin absorption by about 20 percent, so separate the doses by at least 2 hours.
- There are no significant cytochrome P450 interactions, which makes gabapentin useful in patients on complex regimens.
- Use particular caution in COPD, obstructive sleep apnea, heart failure, and any condition already compromising respiratory drive.

SPECIAL POPULATIONS

- Pregnancy data are limited but do not show a clear malformation signal; use the lowest effective dose and document the indication.
- Gabapentin passes into breast milk with a low relative infant dose, and nursing is generally acceptable with infant monitoring.
- Pediatric use is approved for adjunctive seizure therapy from age 3, with weight-based dosing and higher clearance than adults.
- Older adults need dose reduction for declining renal function and are the group most affected by sedation, ataxia, and falls.
- Gabapentin is not federally scheduled, but several states classify it as a Schedule V drug or require prescription monitoring.

PRESCRIBING PEARLS

- Dose by creatinine clearance, not by weight; renal impairment is the single most common cause of toxicity.
- Absorption is saturable, so three divided doses deliver more drug than one large dose.
- Combining gabapentin with opioids meaningfully raises overdose risk; document the reason for both.

References

Anton, R. F., Latham, P., Voronin, K., Book, S., Hoffman, M., Prisciandaro, J., & Bristol, E. (2020). Efficacy of gabapentin for the treatment of alcohol use disorder in patients with alcohol withdrawal symptoms: A randomized clinical trial. *JAMA Internal Medicine, 180*(5), 728-736. https://doi.org/10.1001/jamainternmed.2020.0249

Mason, B. J., Quello, S., Goodell, V., Shadan, F., Kyle, M., & Begovic, A. (2014). Gabapentin treatment for alcohol dependence: A randomized clinical trial. *JAMA Internal Medicine, 174*(1), 70-77. https://doi.org/10.1001/jamainternmed.2013.11950

MedlinePlus. (2023). *Gabapentin*. U.S. National Library of Medicine. https://medlineplus.gov/druginfo/meds/a694007.html

Pfizer. (2023). *Neurontin (gabapentin) capsules [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

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

U.S. Department of Veterans Affairs & U.S. Department of Defense. (2021). *VA/DoD clinical practice guideline for the management of substance use disorders*. https://www.healthquality.va.gov/guidelines/MH/sud/

Wiffen, P. J., Derry, S., Bell, R. F., Rice, A. S. C., Tolle, T. R., Phillips, T., & Moore, R. A. (2017). Gabapentin for chronic neuropathic pain in adults. *Cochrane Database of Systematic Reviews*, (6), CD007938. https://doi.org/10.1002/14651858.CD007938.pub4

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.