BENZODIAZEPINE | C-IV

Clonazepam

Klonopin

Long-acting high-potency benzodiazepine for panic and seizures; smoother coverage than alprazolam and easier to taper.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
0.5-4 mg/day PO (panic)	30-40 h	CYP3A4; inactive metabolite	20-60 min; peak 1-4 h

⚠ FDA BOXED WARNING

Concomitant use with opioids may cause profound sedation, respiratory depression, coma, and death. Abuse, misuse, and addiction can lead to overdose and death. Continued use causes physical dependence; abrupt discontinuation or rapid dose reduction can precipitate life-threatening withdrawal reactions.

INDICATIONS

- FDA-approved for panic disorder with or without agoraphobia in adults, with efficacy shown across 6-9 week placebo-controlled trials.
- FDA-approved as monotherapy or adjunct for Lennox-Gastaut syndrome, akinetic and myoclonic seizures, and absence seizures refractory to succinimides.
- Off-label first-line pharmacotherapy for REM sleep behavior disorder, where low bedtime doses reduce dream enactment and injury risk.
- Off-label for catatonia and as a short-term adjunct in acute mania or agitation, though **lorazepam** is preferred when a parenteral route may be needed.
- Off-label for periodic limb movement disorder, restless legs and for akathisia when beta-blockers are ineffective or contraindicated.
- Guidelines keep SSRIs and SNRIs first line in panic disorder, with **clonazepam** used as a bridge during antidepressant titration.

DOSING & TITRATION

- Panic disorder: start **0.25 mg PO twice daily**, increase to 1 mg/day after 3 days, usual target 1-2 mg/day, labeled maximum **4 mg/day**.
- Adult seizures: start 1.5 mg/day in three divided doses, raise by 0.5-1 mg every 3 days to seizure control, maximum **20 mg/day**.
- Children and infants under 10 years or 30 kg: start 0.01-0.03 mg/kg/day divided, maintenance 0.1-0.2 mg/kg/day divided three times daily.
- Available as scored tablets and orally disintegrating tablets; there is no injectable form in the United States, unlike lorazepam or diazepam.
- Older adults and hepatic impairment start at 0.25 mg once or twice daily; avoid in significant liver disease where glucuronidated agents are safer.
- Taper by 0.125-0.25 mg every 1-2 weeks after long use, slowing to 5-10 percent reductions near the end; abrupt stop risks status epilepticus and death.

MECHANISM OF ACTION

- Positive allosteric modulator at the GABA-A benzodiazepine site, increasing chloride channel opening frequency and inhibiting limbic and cortical firing.
- Non-selective subunit binding gives anxiolysis, sedation, anticonvulsant and muscle relaxant effects together rather than separably.
- Potent anticonvulsant action reflects suppression of spike-and-wave discharge in absence seizures and of cortical spread in myoclonic seizures.
- Long receptor occupancy from its extended half-life yields steady plasma levels, which blunts interdose rebound and reduces reinforcement.
- Chronic exposure causes GABA-A receptor downregulation and uncoupling, the substrate for tolerance, dependence and withdrawal hyperexcitability.

PHARMACOKINETICS

- Essentially complete oral absorption with peak concentrations at 1-4 hours; food has no clinically important effect on absorption.
- Elimination half-life is **30-40 hours**, giving once or twice daily dosing and a gentler withdrawal profile than short-acting agents.
- Reduced by CYP3A4 to 7-aminoclonazepam, then acetylated and glucuronidated; metabolites are pharmacologically inactive.
- Because it depends on hepatic oxidation, clearance falls in cirrhosis and in older adults, whereas lorazepam and oxazepam are unaffected.
- Steady state takes 5-7 days, so titration should be no faster than every 3-4 days or accumulation and oversedation follow.

ADVERSE EFFECTS

- Somnolence in about 37 percent, dizziness 8 percent, coordination problems and ataxia 7 percent, plus fatigue and slowed reaction time.
- Cognitive dulling, anterograde amnesia and reduced working memory that accumulate with dose and often go unrecognized by the patient.
- Behavioral disinhibition, irritability and aggression, seen in up to a quarter of children treated for seizures and in some older adults.
- Hypersalivation and increased bronchial secretions in children, which can compromise airway clearance in neurologically impaired patients.
- Falls, hip fracture and delirium in older adults, plus additive respiratory depression and overdose death when combined with opioids or alcohol.
- Withdrawal after abrupt discontinuation includes rebound anxiety, insomnia, psychosis, status epilepticus and death, and may be delayed several days.

MONITORING

- Screen for substance use disorder and query the prescription drug monitoring program before starting and at intervals during ongoing therapy.
- Reassess sedation, gait, cognition and driving safety at every visit, and document that the original indication still justifies continuation.
- No routine labs are required; check CBC and LFTs periodically during long-term anticonvulsant use as the label suggests.
- Serum levels are not used clinically for panic disorder; in epilepsy, dose to seizure control and tolerability rather than to a concentration.
- Co-prescribe naloxone and document the discussion whenever concurrent opioid therapy cannot be avoided.

INTERACTIONS & CAUTIONS

- Strong CYP3A4 inhibitors such as ketoconazole, ritonavir and clarithromycin raise clonazepam exposure and can produce marked sedation.
- Carbamazepine, phenytoin, phenobarbital and rifampin induce CYP3A4 and can lower levels enough to cause breakthrough seizures or panic.
- Additive CNS and respiratory depression with opioids, alcohol, gabapentinoids, sedating antihistamines and other benzodiazepines or hypnotics.
- Contraindicated in significant hepatic disease, acute narrow-angle glaucoma and known benzodiazepine hypersensitivity.
- Combining clonazepam with valproate has been reported to precipitate absence status epilepticus in susceptible patients.

SPECIAL POPULATIONS

- Pregnancy: first-trimester exposure carries a small possible oral cleft signal, and late exposure causes neonatal sedation, hypotonia and withdrawal.
- Lactation: passes into milk in low amounts; monitor the infant for sedation, apnea and poor feeding, especially in preterm neonates.
- Pediatrics: approved for seizure disorders at weight-based dosing, but paradoxical disinhibition and hypersecretion limit tolerability.
- Older adults: the AGS Beers Criteria advise avoiding benzodiazepines in this group given delirium, falls, fractures and crash risk.
- Hepatic impairment: contraindicated in significant liver disease; use lorazepam, oxazepam or temazepam, which are cleared by glucuronidation alone.

PRESCRIBING PEARLS

- The 30-40 hour half-life covers panic without the clock-watching rebound seen with alprazolam.
- Switching alprazolam to equivalent clonazepam first makes a long benzodiazepine taper far more tolerable.
- First-line drug therapy for REM sleep behavior disorder; melatonin is the safer alternative.

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.