BENZODIAZEPINE | C-IV

Alprazolam

Xanax, Xanax XR, Niravam

High-potency short-acting benzodiazepine for panic and anxiety; fast relief but the hardest of the class to taper.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
0.75-4 mg/day PO divided	11 h (6-27 h)	CYP3A4; no active metabolite	15-30 min; peak 1-2 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 anxiety disorder and short-term relief of anxiety symptoms in adults; safety and efficacy are not established below age 18.
- FDA-approved for panic disorder with or without agoraphobia in adults, using either the immediate-release tablet or the extended-release formulation.
- Guidelines place SSRIs and SNRIs first line for panic and generalized anxiety, with **alprazolam** reserved as short-term adjunct during antidepressant onset.
- Off-label for procedural and situational anxiety such as MRI claustrophobia or aviophobia, given as a single dose rather than standing therapy.
- Off-label as brief adjunct for catatonia or severe agitation, though **lorazepam** is the better studied and more practical benzodiazepine for both.
- Not indicated for PTSD; benzodiazepines show no benefit and are associated with worse outcomes and impaired extinction learning in that population.

DOSING & TITRATION

- Anxiety: start **0.25-0.5 mg PO three times daily**, raise at intervals of 3-4 days as tolerated, to a labeled maximum of **4 mg/day** in divided doses.
- Panic disorder: start 0.5 mg three times daily, increase by no more than 1 mg/day every 3-4 days; mean effective dose 5-6 mg/day, maximum **10 mg/day**.
- Extended-release: start 0.5-1 mg once daily in the morning, titrate to a usual 3-6 mg/day, maximum 10 mg/day; swallow whole and do not crush.
- Older adults, debilitated patients and hepatic impairment start at 0.25 mg two or three times daily and titrate only if clearly tolerated.
- Taper by no more than 0.5 mg every three days after short courses; after months of use reduce 5-10 percent every 2-4 weeks with holds as needed.
- Abrupt discontinuation can cause seizures, delirium and death, so never stop this drug outright and never let a prescription lapse unplanned.

MECHANISM OF ACTION

- Positive allosteric modulator at the benzodiazepine site of the GABA-A receptor, increasing chloride channel opening frequency when endogenous GABA is present.
- Non-selective across alpha-1, alpha-2, alpha-3 and alpha-5 subunits, so sedation and amnesia arrive together with anxiolysis and muscle relaxation.
- High receptor potency and rapid CNS penetration give a fast, perceptible effect that also drives the reinforcing subjective high and misuse liability.
- Tolerance to sedative and anticonvulsant effects develops faster than to anxiolytic effect; receptor adaptation underlies dependence and rebound anxiety.
- Suppresses limbic and brainstem arousal circuits without touching monoamine systems, which is why benzodiazepines treat anxiety but not depression.

PHARMACOKINETICS

- Rapidly and near completely absorbed orally with peak levels at 1-2 hours; the XR tablet peaks near 9 hours and gives a flatter once-daily profile.
- Mean elimination half-life is about **11 hours**, far shorter than clonazepam or diazepam, producing interdose rebound and three-times-daily dosing.
- Metabolized almost entirely by CYP3A4 to alpha-hydroxyalprazolam and an inactive benzophenone; no clinically meaningful active metabolite accumulates.
- Clearance falls in hepatic cirrhosis, obesity, older age and Asian ancestry, with half-life roughly doubling in alcoholic liver disease.
- Unlike lorazepam, oxazepam and temazepam, alprazolam requires hepatic oxidation, so it is a poor choice when liver function is compromised.

ADVERSE EFFECTS

- Somnolence in roughly 40 percent, fatigue 14 percent, impaired coordination 15 percent, memory impairment 15 percent, dizziness and slurred speech.
- Anterograde amnesia and psychomotor slowing that patients underreport; measurable driving impairment persists into the day after a bedtime dose.
- Falls and hip fracture in older adults, plus delirium, making this a high-yield deprescribing target on any geriatric medication review.
- Paradoxical disinhibition with irritability, agitation or aggression, most common in children, older adults, traumatic brain injury and personality disorder.
- Respiratory depression and death when combined with opioids or alcohol; benzodiazepines appear in a large share of US opioid overdose fatalities.
- Withdrawal produces rebound anxiety, insomnia, tremor, autonomic hyperactivity, psychosis and grand mal seizures, and can be fatal if unmanaged.

MONITORING

- Take a substance use history and check the state prescription monitoring program before the first prescription and periodically during therapy.
- At each visit assess sedation, cognition, falls, driving safety, dose escalation and whether the original indication still justifies continued use.
- No routine laboratory monitoring is required; obtain LFTs when liver disease is suspected and a urine drug screen if diversion or misuse is a concern.
- Set an explicit exit plan at initiation, reassess at 2-4 weeks, then at least every three months, since the label supports short-term use only.
- Co-prescribe naloxone and document the risk discussion whenever an opioid is used concurrently and the combination cannot be avoided.

INTERACTIONS & CAUTIONS

- Contraindicated with ketoconazole and itraconazole; strong CYP3A4 inhibition can more than double alprazolam exposure and precipitate oversedation.
- Ritonavir, clarithromycin, nefazodone, fluvoxamine and grapefruit juice raise levels; start lower and monitor for sedation and confusion.
- Carbamazepine, rifampin, phenytoin and St. John's wort induce CYP3A4 and can drop levels enough to trigger breakthrough panic or withdrawal.
- Additive CNS and respiratory depression with opioids, alcohol, gabapentinoids, sedating antihistamines, muscle relaxants and other hypnotics.
- Also contraindicated in acute narrow-angle glaucoma and in known hypersensitivity to alprazolam or other benzodiazepines.

SPECIAL POPULATIONS

- Pregnancy: associated with neonatal sedation, floppy infant syndrome and neonatal withdrawal after third-trimester exposure; avoid or use lowest effective dose.
- Lactation: small amounts enter breast milk and infant sedation and poor feeding are reported; if a benzodiazepine is needed, lorazepam is preferred.
- Pediatrics: not FDA-approved under age 18, and paradoxical disinhibition plus diversion risk make routine outpatient use hard to justify.
- Older adults: the AGS Beers Criteria advise avoiding benzodiazepines in this group entirely because of delirium, falls, fractures and motor vehicle crashes.
- Hepatic impairment: reduce the dose substantially; lorazepam, oxazepam and temazepam bypass oxidation via glucuronidation and are safer choices.

PRESCRIBING PEARLS

- Short half-life makes alprazolam the hardest benzodiazepine to taper; cross to clonazepam first.
- Interdose rebound anxiety mimics worsening illness and drives escalation, not true disease progression.
- Never stop abruptly after chronic use: withdrawal seizures and delirium can be fatal.

References

American Geriatrics Society Beers Criteria Update Expert Panel. (2023). American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. *Journal of the American Geriatrics Society, 71*(7), 2052-2081. https://doi.org/10.1111/jgs.18372

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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.