BENZODIAZEPINE | C-IV

Chlordiazepoxide

Librium, Librax (with clidinium)

The first benzodiazepine; long-acting with active metabolites, still a mainstay of alcohol withdrawal management.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
15-100 mg/day PO divided	24-48 h; metabolites ~100 h	CYP3A4, CYP2C19	PO 30-60 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 mild to moderate anxiety, for severe anxiety disorders, and for preoperative apprehension and anxiety in adults.
- FDA-approved for symptomatic relief of acute alcohol withdrawal, where its long half-life provides a smooth self-tapering effect.
- Guidelines from ASAM support it as a first-choice agent for alcohol withdrawal in patients with preserved hepatic function.
- Marketed in fixed combination with clidinium for adjunctive treatment of peptic ulcer disease and irritable bowel syndrome.
- Off-label for benzodiazepine cross-tapering and detoxification schedules where gradual, forgiving pharmacokinetics are an advantage.
- Not appropriate as maintenance therapy for anxiety disorders; SSRIs, SNRIs and psychotherapy carry the long-term treatment per guideline.

DOSING & TITRATION

- Mild to moderate anxiety: **5-10 mg PO three or four times daily**; severe anxiety disorders 20-25 mg three or four times daily.
- Alcohol withdrawal: 50-100 mg initially, repeated as needed until agitation is controlled, to a labeled maximum of **300 mg/day**.
- A common symptom-triggered protocol gives 50-100 mg every 6 hours guided by CIWA-Ar score, tapering as autonomic signs settle.
- A fixed-dose alternative is 50 mg every 6 hours for four doses, then 25 mg every 6 hours for eight doses, with breakthrough doses allowed.
- Older adults and debilitated patients: start at **5 mg two to four times daily**; children over 6 years may start at 5 mg two to four times daily.
- Taper by 10-25 percent per week after prolonged use; abrupt discontinuation risks withdrawal seizures, delirium and death.

MECHANISM OF ACTION

- Positive allosteric modulator at the GABA-A benzodiazepine site, raising chloride channel opening frequency in the presence of GABA.
- Cross-tolerance with alcohol at the GABA-A receptor is the pharmacologic basis for substituting it during alcohol withdrawal.
- Suppresses the glutamatergic and autonomic hyperexcitability that emerges when chronic alcohol inhibition is abruptly removed.
- Long-lived active metabolites maintain receptor occupancy for days, blunting symptom breakthrough between doses and easing the taper.
- Non-selective subunit binding yields anxiolysis together with sedation, ataxia, amnesia and anticonvulsant protection against withdrawal seizures.

PHARMACOKINETICS

- Well absorbed orally with peak concentrations at 1-4 hours; intramuscular absorption is slow and erratic and should not be relied on.
- Parent half-life is **24-48 hours**, and the active metabolites desmethylchlordiazepoxide, demoxepam and nordiazepam extend to about 100 hours.
- Oxidized by CYP3A4 and CYP2C19 through a chain of active intermediates before glucuronidation, so hepatic function drives clearance.
- In cirrhosis and in older adults, half-life can more than double and metabolites accumulate for a week, producing delayed oversedation.
- Because it requires hepatic oxidation, lorazepam or oxazepam are preferred for withdrawal management in significant liver disease.

ADVERSE EFFECTS

- Drowsiness, ataxia and confusion are the most frequent effects, particularly in older adults and at the higher withdrawal doses.
- Oversedation and respiratory depression accumulate over days because active metabolites keep building until steady state is reached.
- Falls, hip fracture and delirium in older adults, with the risk extending well beyond the last dose given the long metabolite half-lives.
- Paradoxical excitation, rage reactions and disinhibition, described more often with chlordiazepoxide than with shorter-acting agents.
- Rare hepatic dysfunction, jaundice and blood dyscrasias including agranulocytosis have been reported during prolonged therapy.
- Additive respiratory depression and death with opioids or alcohol; withdrawal after chronic use includes seizures and can be fatal.

MONITORING

- Use CIWA-Ar or a comparable validated scale to drive symptom-triggered dosing and to decide when withdrawal treatment can stop.
- Watch for accumulating sedation on days 2-4 of treatment, since steady state lags the first dose by roughly a week.
- Obtain LFTs and assess for cirrhosis before choosing this agent; switch to lorazepam or oxazepam if hepatic function is impaired.
- Give thiamine before glucose in alcohol withdrawal, and check magnesium, potassium and phosphate along with a metabolic panel.
- Periodic CBC and liver enzymes are advised during prolonged therapy given rare dyscrasias and hepatic reactions.

INTERACTIONS & CAUTIONS

- Additive respiratory depression and overdose death with opioids; also with alcohol, gabapentinoids, antipsychotics and other sedatives.
- Strong CYP3A4 inhibitors such as ketoconazole, ritonavir and clarithromycin increase exposure and prolong an already long half-life.
- Rifampin, carbamazepine and phenytoin induce clearance and can precipitate breakthrough withdrawal symptoms or seizures.
- The clidinium combination adds anticholinergic burden and is contraindicated in glaucoma, prostatic hypertrophy and bladder obstruction.
- Contraindicated in known benzodiazepine hypersensitivity and to be avoided in severe respiratory insufficiency and untreated sleep apnea.

SPECIAL POPULATIONS

- Pregnancy: an increased risk of congenital malformations with first-trimester exposure has been suggested; late exposure causes neonatal withdrawal.
- Lactation: long-acting metabolites accumulate in the nursing infant; lorazepam is a better choice if a benzodiazepine is required.
- Pediatrics: not recommended below 6 years of age, and rarely appropriate above it outside specialist supervision.
- Older adults: the AGS Beers Criteria advise avoiding benzodiazepines, and this long-acting agent is a particularly poor geriatric choice.
- Hepatic impairment: avoid in cirrhosis; lorazepam, oxazepam and temazepam bypass oxidative metabolism and are the safer substitutes.

PRESCRIBING PEARLS

- Long half-life self-tapers alcohol withdrawal but keeps accumulating for days in older patients.
- Switch to lorazepam or oxazepam once cirrhosis or significant hepatic impairment is present.
- Intramuscular absorption is erratic, so use the oral route unless there is no 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.