BENZODIAZEPINE | C-IV

Diazepam

Valium, Diastat, Valtoco, Libervant

Long-acting lipophilic benzodiazepine with fast onset; used for alcohol withdrawal, muscle spasm and seizure clusters.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
2-10 mg PO 2-4 times daily	43-48 h; nordiazepam ~100 h	CYP2C19, CYP3A4	PO 15-60 min; IV 1-3 min

⚠ 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 disorders and short-term relief of anxiety symptoms in adults, and for symptomatic relief in acute alcohol withdrawal.
- FDA-approved as an adjunct for skeletal muscle spasm from local pathology, cerebral palsy, athetosis, stiff-person syndrome and upper motor neuron disorders.
- FDA-approved as an adjunct in convulsive disorders; the injection is used for status epilepticus when lorazepam is unavailable.
- Rectal gel is approved for acute repetitive seizures from age 2, and nasal spray for seizure clusters from age 6, both as rescue therapy.
- Off-label for benzodiazepine cross-tapering, where its long half-life and small dose increments make gradual withdrawal more tolerable.
- Off-label for vertigo, tetanus-related spasm and procedural sedation; anxiety maintenance still belongs to SSRIs and SNRIs by guideline.

DOSING & TITRATION

- Anxiety: **2-10 mg PO two to four times daily** depending on severity; most adults need no more than 40 mg/day, and less is usually enough.
- Alcohol withdrawal: 10 mg three or four times in the first 24 hours, then 5 mg three or four times daily; symptom-triggered dosing is preferred.
- Muscle spasm 2-10 mg three or four times daily; adjunctive seizure use 2-10 mg two to four times daily added to the primary anticonvulsant.
- Rectal gel is dosed 0.2-0.5 mg/kg by age band, and nasal spray 5-20 mg by weight, with one repeat dose allowed and no more than five episodes monthly.
- Older adults, debilitated patients and hepatic impairment start at 2-2.5 mg once or twice daily; avoid entirely in advanced cirrhosis.
- Taper by about 10 percent of the current dose every 2-4 weeks after chronic use; abrupt discontinuation can cause seizures, delirium and death.

MECHANISM OF ACTION

- Positive allosteric modulator at the GABA-A benzodiazepine site, raising chloride channel opening frequency and suppressing neuronal firing.
- Very high lipophilicity produces the fastest brain entry in the class, but rapid redistribution out of brain shortens the effect of a single dose.
- Spinal and supraspinal GABA-A facilitation reduces polysynaptic reflex transmission, which is the basis of its skeletal muscle relaxant effect.
- Long-lived active metabolites give sustained receptor occupancy, self-tapering the drug and smoothing alcohol withdrawal symptom control.
- Chronic exposure downregulates GABA-A receptors and produces cross-tolerance with alcohol, the reason it substitutes so well in withdrawal.

PHARMACOKINETICS

- Oral bioavailability approaches 100 percent with peak levels in 1-1.5 hours; intramuscular absorption is erratic and should be avoided.
- Parent half-life is **43-48 hours** and the active metabolite nordiazepam runs to about 100 hours, so accumulation over days is expected.
- Oxidized by CYP2C19 and CYP3A4 to nordiazepam, then to temazepam and oxazepam, all pharmacologically active before glucuronidation.
- CYP2C19 poor metabolizers, common in East Asian populations, show roughly four-fold higher exposure and need lower starting doses.
- Clearance falls sharply in cirrhosis and in older adults, where half-life can exceed 100 hours, making accumulation and delirium likely.

ADVERSE EFFECTS

- Drowsiness, fatigue, ataxia and muscle weakness are the most common effects and are dose-related; slurred speech and diplopia occur at higher doses.
- Anterograde amnesia and impaired psychomotor performance that carry into the following day because of the long parent and metabolite half-lives.
- Accumulation in older adults produces confusion, gait instability, falls, hip fracture and delirium, often days after the dose looked tolerated.
- Paradoxical excitation, hostility and rage reactions, described most often in children, older adults and patients with brain injury.
- Respiratory depression, hypotension and death when combined with opioids or alcohol; intravenous use adds apnea and thrombophlebitis risk.
- Withdrawal is delayed by days because of long half-life and includes rebound anxiety, psychosis and seizures that can prove fatal.

MONITORING

- Assess sedation, gait and cognition at each visit, remembering that steady state is not reached for 5-10 days after any dose change.
- Screen for substance use disorder and check the prescription drug monitoring program before starting and periodically thereafter.
- Use CIWA-Ar or a similar validated scale to drive symptom-triggered dosing in alcohol withdrawal rather than fixed tapering schedules.
- Check LFTs when liver disease is suspected, and switch to lorazepam or oxazepam if hepatic synthetic function is impaired.
- For rescue formulations, document seizure cluster frequency and confirm caregivers can recognize when emergency care is still required.

INTERACTIONS & CAUTIONS

- Additive respiratory depression and overdose death with opioids; also with alcohol, gabapentinoids, sedating antihistamines and other hypnotics.
- Strong CYP2C19 or CYP3A4 inhibitors such as omeprazole, fluvoxamine, fluconazole, ketoconazole and ritonavir raise levels substantially.
- Rifampin, carbamazepine, phenytoin and St. John's wort induce clearance and may cause breakthrough seizures or withdrawal symptoms.
- Contraindicated in acute narrow-angle glaucoma, myasthenia gravis, severe respiratory insufficiency, sleep apnea and severe hepatic insufficiency.
- Concurrent clozapine has been associated with collapse and respiratory arrest; introduce one drug at a time and monitor closely.

SPECIAL POPULATIONS

- Pregnancy: crosses the placenta freely; third-trimester use causes floppy infant syndrome and neonatal withdrawal lasting days to weeks.
- Lactation: diazepam and nordiazepam accumulate in the nursing infant because of immature clearance; prefer lorazepam if a benzodiazepine is required.
- Pediatrics: oral use is not recommended under 6 months; rescue rectal gel is approved from age 2 and nasal spray from age 6.
- Older adults: the AGS Beers Criteria advise avoiding benzodiazepines, and diazepam is among the worst choices given metabolite accumulation.
- Hepatic impairment: contraindicated in severe disease; lorazepam, oxazepam and temazepam avoid oxidation and are the appropriate substitutes.

PRESCRIBING PEARLS

- Fast in, fast out of brain: a single IV dose wears off quickly despite a 48-hour half-life.
- Long half-life self-tapers, which is why it suits alcohol withdrawal but not older adults.
- CYP2C19 poor metabolizers, common in East Asian patients, reach roughly four-fold higher levels.

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

American Society of Addiction Medicine. (2020). *The ASAM clinical practice guideline on alcohol withdrawal management*. https://www.asam.org/quality-care/clinical-guidelines/alcohol-withdrawal-management-guideline

Glauser, T., Shinnar, S., Gloss, D., Alldredge, B., Arya, R., Bainbridge, J., Bare, M., Bleck, T., Dodson, W. E., Garrity, L., Jagoda, A., Lowenstein, D., Pellock, J., Riviello, J., Sloan, E., & Treiman, D. M. (2016). Evidence-based guideline: Treatment of convulsive status epilepticus in children and adults. *Epilepsy Currents, 16*(1), 48-61. https://doi.org/10.5698/1535-7597-16.1.48

National Institute for Health and Care Excellence. (2020). *Generalised anxiety disorder and panic disorder in adults: Management* (Clinical guideline CG113). https://www.nice.org.uk/guidance/cg113

Roche Laboratories. (2023). *Valium (diazepam) [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Stahl, S. M. (2021). *Stahl's essential psychopharmacology* (5th ed.). Cambridge University Press.

U.S. National Library of Medicine. (2021). *Diazepam*. MedlinePlus. https://medlineplus.gov/druginfo/meds/a682047.html

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.