ALPHA-2 ADRENERGIC AGONIST

Clonidine

Catapres, Catapres-TTS, Kapvay, Onyda XR, Duraclon

Nonselective alpha-2 agonist used for ADHD, tics, withdrawal states, and sleep onset; more sedating and hypotensive than guanfacine.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
0.1-0.4 mg/day PO divided	12-16 h; up to 41 h in ESRD	Hepatic; ~50% renal unchanged	30-60 min; peak 1-3 h

No FDA boxed warning on the current US label.

INDICATIONS

- Kapvay extended-release tablets are FDA-approved for ADHD in patients age 6 to 17 years as monotherapy or as adjunct to stimulants.
- Onyda XR, an extended-release oral suspension approved in 2024, is the first liquid nonstimulant for ADHD in patients age 6 and older.
- Immediate-release tablets and the transdermal patch are approved for hypertension in adults and are not approved for ADHD.
- Used off-label for opioid and alcohol withdrawal, where it blunts autonomic hyperactivity, sweating, and restlessness.
- Used off-label for tics and Tourette syndrome, PTSD hyperarousal and nightmares, and sleep-onset insomnia in children with ADHD.
- Epidural clonidine is approved as an adjunct for severe cancer pain, and that formulation carries its own boxed warning against obstetric and perioperative use.

DOSING & TITRATION

- Kapvay for ADHD: start **0.1 mg** PO at bedtime, increase by 0.1 mg/day weekly to a maximum of **0.4 mg/day**, given in two divided doses.
- When divided doses are unequal, give the larger portion at bedtime to concentrate sedation during sleep rather than during school.
- Onyda XR is dosed once daily at bedtime, starting at **0.1 mg** and titrating weekly by 0.1 mg to a maximum of 0.4 mg/day.
- Immediate-release clonidine for hypertension in adults: start **0.1 mg** PO twice daily, usual range 0.2-0.6 mg/day, maximum 2.4 mg/day.
- Opioid withdrawal off-label: **0.1-0.2 mg** PO every 6-8 hours as tolerated, holding for systolic pressure below 90 mmHg.
- Taper by no more than **0.1 mg every 3 to 7 days**, since abrupt withdrawal can cause rebound hypertension and severe agitation.

MECHANISM OF ACTION

- Agonist at presynaptic alpha-2 autoreceptors in the locus coeruleus, reducing central noradrenergic firing and sympathetic outflow.
- Also stimulates postsynaptic alpha-2A receptors in prefrontal cortex, the action shared with guanfacine that improves impulse control.
- It is nonselective across alpha-2A, alpha-2B, and alpha-2C subtypes, which accounts for greater sedation and hypotension than guanfacine.
- Reduced noradrenergic tone explains its benefit in opioid withdrawal, where autonomic symptoms arise from locus coeruleus hyperactivity.
- Partial imidazoline receptor activity contributes to the blood pressure lowering effect and to rebound hypertension on withdrawal.

PHARMACOKINETICS

- Immediate-release Tmax is 1-3 hours; the extended-release formulations shift peak later and reduce peak sedation.
- Half-life is 12-16 hours in normal renal function and can extend to 41 hours in end-stage renal disease.
- About half the dose is excreted unchanged in urine and the rest is metabolized hepatically, with minor CYP2D6 involvement.
- Bioavailability of oral clonidine is 70-80 percent, and the transdermal patch delivers steady concentrations over 7 days.
- Extended-release and immediate-release forms are not interchangeable on a milligram basis and require separate titration.

ADVERSE EFFECTS

- Somnolence in 30-40 percent, fatigue, dry mouth, headache, and irritability are the most frequent effects and often limit titration.
- Hypotension, orthostatic dizziness, and bradycardia are dose related and more pronounced than with guanfacine.
- Rebound hypertension, tachycardia, tremor, and agitation follow abrupt discontinuation, especially at higher antihypertensive doses.
- Depressed mood, vivid dreams, and blunted affect are reported and can be mistaken for worsening of the underlying psychiatric disorder.
- Overdose in young children is dangerous, producing bradycardia, hypotension, miosis, and respiratory depression that mimics opioid toxicity.
- Transdermal use adds contact dermatitis, which affects a meaningful minority of patients using the weekly patch.

MONITORING

- Baseline and periodic heart rate and blood pressure, including orthostatic measurements in patients reporting dizziness or falls.
- Ask about daytime sedation and school or work performance, since sedation is the dominant reason clonidine fails in practice.
- Track ADHD or tic severity with a validated scale at baseline and after 4-6 weeks at a stable dose.
- Verify that patients and families understand that missed doses risk rebound hypertension and that stopping requires a taper.
- Reassess renal function in older adults and in patients with chronic kidney disease, since the half-life lengthens substantially.

INTERACTIONS & CAUTIONS

- Additive hypotension and bradycardia with beta-blockers, calcium channel blockers, digoxin, and other antihypertensives.
- Beta-blockers can worsen rebound hypertension during clonidine withdrawal, so stop the beta-blocker first when both are being discontinued.
- Tricyclic antidepressants and mirtazapine antagonize the antihypertensive effect through alpha-2 receptor blockade.
- Additive central nervous system depression with alcohol, benzodiazepines, opioids, and sedating antihistamines.
- Combining with stimulants is common and generally safe, but blood pressure and heart rate should still be tracked at each visit.

SPECIAL POPULATIONS

- Pregnancy: limited human data with no clear teratogenic pattern; it is sometimes continued for hypertension when alternatives are unsuitable.
- Lactation: clonidine is present in human milk and can reduce milk supply, so monitor infant sedation and maternal lactation closely.
- Pediatric: extended-release forms are approved from age 6, and accidental ingestion by toddlers is a recognized poisoning emergency.
- Geriatric: start at the lowest dose because of orthostatic hypotension, falls, sedation, and reduced renal clearance.
- Renal impairment: reduce the dose and extend the interval, since roughly half of the drug is cleared unchanged by the kidney.

PRESCRIBING PEARLS

- Clonidine sedates far more than guanfacine; put the bigger share of the dose at bedtime.
- Never stop it abruptly, and stop any beta-blocker first to avoid rebound hypertension.
- A toddler who swallows one tablet can look opioid-poisoned; treat every ingestion as serious.

References

Cortese, S. (2020). Pharmacologic treatment of attention deficit-hyperactivity disorder. *New England Journal of Medicine, 383*(11), 1050-1056. https://doi.org/10.1056/NEJMra1917069

Jain, R., Segal, S., Kollins, S. H., & Khayrallah, M. (2011). Clonidine extended-release tablets for pediatric patients with attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry, 50*(2), 171-179. https://doi.org/10.1016/j.jaac.2010.11.005

Kollins, S. H., Jain, R., Brams, M., Segal, S., Findling, R. L., Wigal, S. B., & Khayrallah, M. (2011). Clonidine extended-release tablets as add-on therapy to psychostimulants in children and adolescents with ADHD. *Pediatrics, 127*(6), e1406-e1413. https://doi.org/10.1542/peds.2010-1260

National Institute for Health and Care Excellence. (2018). *Attention deficit hyperactivity disorder: Diagnosis and management* (NICE guideline NG87). https://www.nice.org.uk/guidance/ng87

National Institute of Diabetes and Digestive and Kidney Diseases. (2020). Clonidine. In *LiverTox: Clinical and research information on drug-induced liver injury*. https://www.ncbi.nlm.nih.gov/books/NBK548329/

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

Tris Pharma. (2024). *Onyda XR (clonidine hydrochloride) extended-release oral suspension [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

Wolraich, M. L., Hagan, J. F., Allan, C., Chan, E., Davison, D., Earls, M., Evans, S. W., Flinn, S. K., Froehlich, T., Frost, J., Holbrook, J. R., Lehmann, C. U., Lessin, H. R., Okechukwu, K., Pierce, K. L., Winner, J. D., & Zurhellen, W. (2019). Clinical practice guideline for the diagnosis, evaluation, and treatment of attention-deficit/hyperactivity disorder in children and adolescents. *Pediatrics, 144*(4), e20192528. https://doi.org/10.1542/peds.2019-2528

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.