STIMULANT C-II

# Methylphenidate

Ritalin, Ritalin LA, Concerta, Metadate ER, Methylin, Daytrana, Quillivant XR, QuilliChew ER, Aptensio XR, Cotempla XR-ODT, Jornay PM, Relexxii

*First-line stimulant for ADHD across the lifespan; a dopamine and norepinephrine reuptake blocker sold in a dozen delivery systems.*

| USUAL ADULT RANGE | HALF-LIFE | METABOLISM | ONSET |
|---|---|---|---|
| IR 20-60 mg/day; ER 18-72 mg/day | 2-3 h IR; 3.5-4 h OROS | CES1A1 de-esterification | 30-60 min; peak 1-3 h |

**FDA BOXED WARNING**

Abuse, misuse, addiction, and dependence: methylphenidate has a high potential for abuse and misuse that can lead to substance use disorder including addiction; misuse, especially at high doses or by snorting or injection, can cause overdose and death. Assess risk before prescribing and monitor throughout treatment.

## INDICATIONS

- FDA-approved for attention-deficit/hyperactivity disorder in children age 6 years and older, adolescents, and adults across immediate- and extended-release products.
- FDA-approved for narcolepsy in patients age 6 and older, usually with immediate-release tablets given two or three times daily.
- Extended-release products such as Concerta, Ritalin LA, and Jornay PM give one dose per day covering the school or work day without a midday dose.
- Used off-label to augment antidepressants in treatment-resistant depression, especially for apathy and fatigue in geriatric or medically ill adults.
- Used off-label for cancer-related fatigue, opioid-induced sedation, and apathy or cognitive slowing after traumatic brain injury or stroke.
- Off-label in preschoolers aged 4-5 years with ADHD when parent training in behavior management has failed, per AAP guidance.

## DOSING & TITRATION

- Immediate-release: start **5 mg** PO twice daily before breakfast and lunch, raise by **5-10 mg/day** weekly, to a maximum of **60 mg/day** divided.
- Concerta OROS: start **18 mg** PO every morning and titrate weekly by 18 mg; max **54 mg/day** in children 6-12 and **72 mg/day** in teens and adults.
- Ritalin LA and Aptensio XR start at **10-20 mg** each morning; Jornay PM is taken in the evening starting at **20 mg** for next-morning onset, max 100 mg/day.
- Daytrana patch starts at **10 mg/9 h** applied 2 hours before effect is needed and removed after 9 hours; titrate weekly through 15, 20, and 30 mg patches.
- No renal or hepatic adjustment is labeled; hold or reduce dose for weight loss, insomnia, or rising blood pressure rather than pushing the dose higher.
- No pharmacologic taper is needed, but stopping chronic high doses abruptly can unmask fatigue, hyperphagia, and depressed mood for several days.

## MECHANISM OF ACTION

- Blocks the dopamine transporter and the norepinephrine transporter, raising synaptic dopamine and norepinephrine in prefrontal cortex and striatum.
- Unlike amphetamines it does not appreciably reverse transporter flux or empty vesicular stores, so release stays activity-dependent rather than forced.
- Prefrontal norepinephrine at postsynaptic alpha-2A receptors and dopamine at D1 receptors sharpens signal-to-noise in working memory circuits.
- The d-threo enantiomer carries nearly all activity; racemic methylphenidate is about half largely inert l-threo isomer removed on first pass.
- Striatal transporter occupancy near 50 percent tracks response, and slow-rising delivery systems blunt the euphoria that drives abuse liability.

## PHARMACOKINETICS

- Rapidly absorbed orally with immediate-release Tmax of 1-2 hours; food delays peak modestly but does not reduce total absorption of most products.
- Cleared by presystemic and hepatic de-esterification via carboxylesterase CES1A1 to inactive ritalinic acid, so clinically important CYP interactions are rare.
- Elimination half-life is 2-3 hours for immediate-release and 3.5-4 hours for OROS, yet duration of effect is set by the delivery system, not the half-life.
- Protein binding is low at 10-33 percent, volume of distribution is about 2.65 L/kg, and roughly 80 percent is excreted renally as ritalinic acid.
- The Daytrana transdermal patch bypasses first-pass metabolism and gives higher d-methylphenidate exposure than the same oral milligram dose.

## ADVERSE EFFECTS

- Decreased appetite in 25-35 percent, insomnia in 12-20 percent, headache, abdominal pain, irritability, and dry mouth are the usual dose-related effects.
- Mean rises of about 2-4 mmHg in blood pressure and 3-6 bpm in heart rate; a minority develop clinically meaningful hypertension or tachycardia.
- Growth velocity slows by roughly 1-2 cm and 1-3 kg over the first 1-3 years of continuous treatment in children, with partial catch-up afterward.
- New psychosis or mania occurs in about 0.1 percent; hallucinations at usual doses call for stopping the stimulant rather than adding an antipsychotic.
- Priapism, peripheral vasculopathy including Raynaud phenomenon, and emergent motor or vocal tics are labeled warnings that usually prompt a change.
- Sudden cardiac death has been reported in patients with structural cardiac disease, so screen personal and family cardiac history before starting.

## MONITORING

- Baseline height, weight, blood pressure, pulse, cardiac and family sudden-death history, plus screening for tics, psychosis, and substance misuse.
- Recheck pulse, blood pressure, and weight at each visit and plot height and weight on growth charts at least every 6 months in children.
- Track response with a validated scale such as ADHD-RS-5, Vanderbilt, or Conners at baseline and after every dose change rather than by impression alone.
- Routine ECG and laboratory monitoring are not required; obtain ECG or cardiology input only when history, exam, or symptoms suggest cardiac disease.
- Reassess diversion risk, early refill requests, and lost prescriptions at every visit and check the state prescription drug monitoring program.

## INTERACTIONS & CAUTIONS

- Contraindicated within 14 days of an MAOI including phenelzine, tranylcypromine, selegiline, and linezolid because of hypertensive crisis risk.
- CYP-mediated interactions are minimal, but methylphenidate can inhibit clearance of warfarin, phenytoin, and tricyclic antidepressants, raising levels.
- Additive sympathomimetic effects with decongestants, other stimulants, and SNRIs raise blood pressure and heart rate; monitor vitals when combined.
- Halogenated anesthetics can trigger abrupt blood pressure and heart rate rises, so hold the stimulant on the morning of elective surgery.
- Gastric alkalinizers speed release of some ER capsules while acidifying agents slow absorption; the effect is smaller than it is with amphetamines.

## SPECIAL POPULATIONS

- Pregnancy: no clear teratogenic signal, though registry data suggest a small absolute rise in cardiac malformations; continue only if benefit outweighs risk.
- Lactation: transferred in small amounts with relative infant dose under 1 percent, so it is generally considered compatible with breastfeeding.
- Pediatric: labeled from age 6 years; preschool use is off-label and behavioral parent training should be tried first per AAP guidance.
- Geriatric: start at the low end and watch blood pressure, arrhythmia, anorexia, and delirium; evidence for apathy in dementia remains limited.
- No dose change is required in renal or hepatic impairment because clearance depends on plasma and tissue carboxylesterase rather than liver or kidney.

## PRESCRIBING PEARLS

- Duration of action, not half-life, drives product choice; match the delivery system to the patient's day.
- Failing methylphenidate does not predict failing amphetamine; roughly 40 percent respond to the other class.
- Manage appetite loss by feeding around the dose rather than by lowering an otherwise effective dose.

# 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

Cortese, S., Adamo, N., Del Giovane, C., Mohr-Jensen, C., Hayes, A. J., Carucci, S., Atkinson, L. Z., Tessari, L., Banaschewski, T., Coghill, D., Hollis, C., Simonoff, E., Zuddas, A., Barbui, C., Purgato, M., Steinhausen, H. C., Shokraneh, F., Xia, J., & Cipriani, A. (2018). Comparative efficacy and tolerability of medications for attention-deficit hyperactivity disorder in children, adolescents, and adults: A systematic review and network meta-analysis. *The Lancet Psychiatry, 5*(9), 727-738. https://doi.org/10.1016/S2215-0366(18)30269-4

MedlinePlus. (2024). *Methylphenidate*. U.S. National Library of Medicine. https://medlineplus.gov/druginfo/meds/a682188.html

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

Novartis Pharmaceuticals. (2023). *Ritalin (methylphenidate hydrochloride) [Prescribing information]*. U.S. Food and Drug Administration. https://dailymed.nlm.nih.gov/dailymed/

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

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.