SECOND-GENERATION ANTIPSYCHOTIC

Risperidone

Risperdal, Risperdal M-Tab, Risperdal Consta, Perseris, Uzedy, Rykindo

High-potency D2 and 5-HT2A blocker; efficacy is reliable but prolactin elevation and dose-dependent EPS limit it.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
2-8 mg/day PO	3 h (20 h active moiety)	CYP2D6 to paliperidone	1-2 wks; 4-6 wks full

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; risperidone is not approved for the treatment of patients with dementia-related psychosis.

INDICATIONS

- Schizophrenia in adults and in adolescents ages 13-17, both acutely and for maintenance, with long-acting injectables approved for maintenance therapy.
- Acute manic or mixed episodes of bipolar I disorder in patients ages 10-17 and in adults, as monotherapy or as adjunct to lithium or valproate in adults.
- Irritability associated with autistic disorder, including aggression, deliberate self-injury, and temper tantrums, in children ages 5-16.
- Risperdal Consta is also approved as monotherapy or adjunct to lithium or valproate for maintenance treatment of bipolar I disorder in adults.
- Off-label uses include Tourette's disorder, treatment-resistant depression augmentation, and short-term management of agitation in delirium.

DOSING & TITRATION

- Schizophrenia in adults: start **2 mg/day PO**, increase to 4 mg on day 2, target **4-8 mg/day**, with a labeled maximum of **16 mg/day**.
- Efficacy plateaus near 6 mg/day while extrapyramidal symptoms climb steeply above it, so most patients should stay at or below that dose.
- Adolescents with schizophrenia start **0.5 mg/day** and target 3 mg/day; autism-related irritability starts at 0.25-0.5 mg/day by body weight.
- Risperdal Consta is **12.5-50 mg IM every 2 weeks** with 3 weeks of oral overlap; Uzedy is subcutaneous monthly or every 2 months without overlap.
- In renal or hepatic impairment start **0.5 mg twice daily** and titrate in 0.5 mg increments no faster than weekly above 1.5 mg twice daily.
- Taper over weeks when stopping, since the short parent half-life makes abrupt discontinuation prone to rebound psychosis and cholinergic rebound.

MECHANISM OF ACTION

- Potent antagonist at dopamine **D2** receptors, giving reliable antipsychotic efficacy but a steep dose-dependent rise in extrapyramidal symptoms.
- Even more potent **5-HT2A** antagonism, which softens striatal D2 blockade at low doses and contributes to effect on negative symptoms.
- Strong alpha-1 and alpha-2 adrenergic blockade produces orthostatic hypotension, dizziness, and reflex tachycardia during titration.
- Tuberoinfundibular D2 blockade raises prolactin more than any other second-generation agent except paliperidone, its own active metabolite.
- Moderate histamine H1 affinity gives sedation and appetite stimulation, but muscarinic affinity is negligible.

PHARMACOKINETICS

- Well absorbed orally with about 70 percent bioavailability, unaffected by food, and available as tablet, orally disintegrating tablet, and solution.
- **CYP2D6** converts risperidone to 9-hydroxyrisperidone, which is paliperidone and is equally active, so the two drugs share a pharmacology.
- Half-life is about 3 hours for parent drug but roughly **20 hours** for the active moiety, extending to 24 hours in CYP2D6 poor metabolizers.
- Renal clearance dominates for the active metabolite, so creatinine clearance below **30 mL/min** roughly doubles exposure.
- Steady state is reached in about 5 days on oral dosing but takes 4-6 weeks for the long-acting injectable formulations.

ADVERSE EFFECTS

- Hyperprolactinemia is near universal at higher doses, causing amenorrhea, galactorrhea, gynecomastia, sexual dysfunction, and bone density loss.
- Extrapyramidal symptoms including akathisia, parkinsonism, and dystonia rise sharply above **6 mg/day** and often require a dose reduction.
- Weight gain is moderate at roughly **2-4 kg** over the first months, with intermediate risk of dyslipidemia and glucose dysregulation.
- Sedation, orthostatic hypotension, dizziness, and tachycardia are common early and are the main reason for slow initial titration.
- Tardive dyskinesia, neuroleptic malignant syndrome, and rare priapism from alpha blockade are the serious events that change prescribing.

MONITORING

- Weight, BMI, and blood pressure at baseline and each visit early on, with fasting glucose or A1c and lipids at baseline, 12 weeks, and annually.
- Check a prolactin level whenever amenorrhea, galactorrhea, gynecomastia, or sexual dysfunction appears, rather than screening everyone.
- AIMS at baseline and every 6-12 months, more often in older adults, women, and anyone with a history of extrapyramidal reactions.
- Orthostatic vital signs during titration and after any dose increase, especially in older or volume-depleted patients.
- Consider bone density assessment in patients with prolonged hyperprolactinemia and amenorrhea or hypogonadism.

INTERACTIONS & CAUTIONS

- **CYP2D6** inhibitors such as fluoxetine, paroxetine, and bupropion raise the active moiety substantially and may require a dose reduction.
- **Carbamazepine** and other strong inducers can cut the active moiety by half; increase the dose and reverse the change when the inducer stops.
- Additive hypotension with antihypertensives and additive sedation with benzodiazepines, opioids, alcohol, and other CNS depressants.
- Risperidone antagonizes levodopa and other dopamine agonists, making it a poor choice in Parkinson disease psychosis.
- QT prolongation is modest but additive with other QT-prolonging drugs and with electrolyte depletion from diuretics.

SPECIAL POPULATIONS

- Third-trimester exposure carries risk of neonatal extrapyramidal and withdrawal symptoms; the National Pregnancy Registry tracks outcomes.
- Excreted into breast milk at low relative infant dose, so breastfeeding is generally acceptable with monitoring for infant sedation.
- Approved from age 5 for autism-related irritability, where weight gain, sedation, and prolactin elevation are more pronounced than in adults.
- In older adults start at **0.25-0.5 mg/day** and titrate slowly given fall risk, orthostasis, and the dementia mortality warning.
- Reduce the starting dose and titration rate in renal impairment with creatinine clearance under **30 mL/min** and in hepatic impairment.

PRESCRIBING PEARLS

- Above 6 mg/day you buy extrapyramidal symptoms, not efficacy; go up only with clear evidence of benefit.
- Any new amenorrhea or galactorrhea should trigger a prolactin level and a switch, not reassurance.
- Risperidone is a prodrug for paliperidone, so a paliperidone switch is a formulation change.

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.