FIRST-GENERATION ANTIPSYCHOTIC

Haloperidol

Haldol, Haldol Decanoate

High-potency butyrophenone antipsychotic; the reference agent for acute agitation, Tourette syndrome, and long-acting FGA maintenance.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
1-15 mg/day PO; max 30 mg/day	~18 h PO; ~3 wks decanoate	CYP3A4, CYP2D6, glucuronidation	IM 30-60 min; 1-2 wks psychosis

⚠ FDA BOXED WARNING

Increased mortality in elderly patients with dementia-related psychosis treated with antipsychotic drugs; haloperidol is not approved for dementia-related psychosis.

INDICATIONS

- FDA-approved for schizophrenia in adults, including the decanoate depot for patients requiring prolonged parenteral antipsychotic therapy.
- FDA-approved for control of tics and vocal utterances of Tourette syndrome in adults and in children aged 3 years and older.
- FDA-approved for severe behavior problems and short-term treatment of hyperactivity in children aged 3 to 12 years unresponsive to other agents.
- Off-label mainstay for acute undifferentiated agitation, often given IM with lorazepam, and for agitated hyperactive delirium in medically ill adults.
- Off-label use in acute bipolar mania as adjunct to a mood stabilizer, and off-label IV use for refractory nausea or intractable hiccups.
- Off-label first-line for chorea and severe behavioral disturbance in Huntington disease when a VMAT2 inhibitor is unavailable or ineffective.

DOSING & TITRATION

- Oral start is **0.5-2 mg** two or three times daily for moderate symptoms; severe or chronic illness may begin at **3-5 mg** two or three times daily.
- Titrate every 1-3 days by clinical response to a usual target of **5-15 mg/day**; doses above **30 mg/day** rarely add benefit and sharply raise EPS.
- Acute agitation is typically **2-5 mg IM** repeated every 4-8 hours as needed; elderly or delirious patients start at **0.25-0.5 mg** per dose.
- Decanoate initial dose is 10-20 times the stabilized oral daily dose, capped at **100 mg** for the first injection, then given every 4 weeks.
- No formal renal adjustment; reduce and titrate slowly in hepatic impairment since clearance falls and free drug rises with low albumin.
- Taper oral therapy over weeks rather than stopping abruptly to avoid cholinergic rebound, insomnia, and withdrawal dyskinesia.

MECHANISM OF ACTION

- Potent postsynaptic dopamine D2 receptor antagonist; roughly 65-80 percent striatal D2 occupancy gives antipsychotic effect with acceptable motor burden.
- Occupancy above about 80 percent drives acute dystonia, akathisia, and parkinsonism, so higher doses add extrapyramidal risk without more efficacy.
- Tuberoinfundibular D2 blockade removes dopaminergic brake on prolactin, producing dose-dependent hyperprolactinemia, amenorrhea, and sexual dysfunction.
- Negligible muscarinic and histamine H1 affinity explains the low sedation and dry mouth relative to chlorpromazine, but also the high extrapyramidal rate.
- Weak alpha-1 antagonism means less orthostasis than low-potency phenothiazines; the parent drug and reduced haloperidol both block hERG potassium channels.

PHARMACOKINETICS

- Oral bioavailability is 60-70 percent with first-pass metabolism; IM lactate peaks in 20-40 minutes and gives essentially complete absorption.
- Elimination half-life is about 18 hours after oral dosing (range 14-37 h) and roughly 21 days for the decanoate, which reaches steady state in 2-3 months.
- Metabolized by CYP3A4 and CYP2D6 plus glucuronidation; reduced haloperidol is an interconverting metabolite with minimal antipsychotic activity.
- Highly protein bound at about 90 percent and extensively distributed, so dialysis does not meaningfully remove the drug during overdose.
- It is a moderate CYP2D6 inhibitor, so plasma concentrations of 2D6 substrates such as venlafaxine or tricyclics can rise during co-administration.

ADVERSE EFFECTS

- Extrapyramidal symptoms are the dominant burden: acute dystonia in up to 10 percent, akathisia in 20-40 percent, and parkinsonism in 20-30 percent.
- Tardive dyskinesia accrues at roughly 4-5 percent per year of exposure in nonelderly adults and several times that rate in older patients.
- Neuroleptic malignant syndrome is rare but disproportionately reported with high-potency agents; fever, rigidity, autonomic lability, and high creatine kinase.
- Hyperprolactinemia is common and symptomatic, causing galactorrhea, menstrual disruption, sexual dysfunction, and long-term bone density loss.
- QT prolongation and torsades de pointes occur mainly with intravenous or high cumulative dosing; IV administration is not an FDA-approved route.
- Metabolic effects and weight gain are modest compared with second-generation agents; sedation and orthostasis are relatively mild.

MONITORING

- Baseline and periodic extrapyramidal exam with a formal AIMS every 6 months, or every 3 months in patients at high tardive dyskinesia risk.
- ECG at baseline and after dose increases when cardiac disease, electrolyte disturbance, other QT drugs, or parenteral dosing is involved.
- Check potassium and magnesium before parenteral or high-dose therapy and correct deficits, since hypokalemia amplifies torsades risk.
- Prolactin only if symptomatic; obtain CBC in the first months when baseline neutrophil count is low or there is a history of drug-induced leukopenia.
- Weight, blood pressure, glucose, and lipids at baseline and annually, plus creatine kinase whenever rigidity or unexplained fever appears.

INTERACTIONS & CAUTIONS

- Strong CYP3A4 inducers such as carbamazepine, rifampin, and phenytoin can halve haloperidol levels and precipitate loss of symptom control.
- CYP2D6 inhibitors including fluoxetine, paroxetine, and bupropion raise concentrations and extrapyramidal risk, warranting a lower dose.
- Additive QT risk with methadone, ondansetron, fluoroquinolones, azole antifungals, and class III antiarrhythmics; avoid or monitor with ECG.
- Rare encephalopathic syndrome with confusion and cerebellar signs has been reported when haloperidol is combined with lithium at high levels.
- Contraindicated in severe CNS depression, comatose states, Parkinson disease, dementia with Lewy bodies, and known haloperidol hypersensitivity.

SPECIAL POPULATIONS

- In pregnancy it is among the better-characterized antipsychotics; third-trimester exposure carries a class risk of neonatal EPS and withdrawal signs.
- Excreted into breast milk in low relative infant dose; breastfeeding is usually acceptable with monitoring for infant sedation and motor signs.
- Pediatric use is labeled from age 3; dose by weight starting at **0.5 mg/day** and titrate in 0.5 mg increments given the high dystonia risk.
- In older adults use one-quarter to one-half the adult dose; dementia-related psychosis carries the boxed mortality warning and no approval.
- Renal impairment needs no adjustment, but hepatic impairment or hypoalbuminemia raises free drug and warrants slower, lower dosing.

PRESCRIBING PEARLS

- IM lorazepam **1-2 mg** with haloperidol cuts total antipsychotic dose and blunts akathisia and dystonia.
- Keep IM benztropine or diphenhydramine at hand; acute dystonia peaks in the first 24-72 hours.
- Decanoate takes 2-3 months to reach steady state, so overlap oral therapy rather than chasing doses.

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.