FIRST-GENERATION ANTIPSYCHOTIC

Chlorpromazine

Thorazine (brand discontinued; generic only)

Low-potency phenothiazine and the first antipsychotic; now reserved for agitation, hiccups, and nausea where sedation is acceptable.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
200-800 mg/day PO divided	**~30 h; active metabolites**	**CYP2D6 > 1A2, 3A4; hepatic**	**IM 15-30 min; 1-2 wks psychosis**

⚠ FDA BOXED WARNING

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

INDICATIONS

- FDA-approved for schizophrenia and for the manic phase of bipolar disorder in adults, and for severe behavioral disturbance in children aged 1 to 12.
- FDA-approved for nausea and vomiting, intractable hiccups, and preoperative restlessness in adults, usually at doses well below antipsychotic range.
- FDA-approved as adjunctive therapy in tetanus and for the acute intermittent porphyria attack, reflecting its long and broad legacy labeling.
- Off-label use for acute agitation when marked sedation is desirable and for refractory nausea in palliative care at low divided doses.
- Off-label option for status migrainosus and severe cyclic vomiting, typically given parenterally with a fluid bolus to offset hypotension.
- No longer a first-line antipsychotic; guidelines favor higher-potency or second-generation agents because of its sedation and autonomic load.

DOSING & TITRATION

- For psychosis, start **10-25 mg** orally three or four times daily and increase by 20-50 mg every 3-4 days to a usual **200-800 mg/day**.
- Severe refractory illness may require up to **2000 mg/day**, but exposure at that level markedly increases hypotension, sedation, and seizure risk.
- Acute agitation can be treated with **25 mg IM**, repeated at 25-50 mg after one hour if needed, with the patient supine and blood pressure checked.
- Intractable hiccups and nausea respond to **25-50 mg** orally three or four times daily, far below the antipsychotic dose range.
- No specific renal adjustment; halve the starting dose and titrate slowly in hepatic impairment, and avoid it entirely in decompensated liver disease.
- Discontinue by tapering over several weeks; abrupt withdrawal provokes cholinergic rebound with nausea, insomnia, sweating, and dyskinesias.

MECHANISM OF ACTION

- Antagonizes dopamine D2 receptors with only moderate affinity, so effective antipsychotic doses are ten to twenty times those of haloperidol.
- Strong alpha-1 adrenergic blockade produces the orthostatic hypotension, reflex tachycardia, nasal congestion, and priapism seen at higher doses.
- Potent histamine H1 antagonism drives the pronounced sedation and appetite gain that made it useful for agitation before newer agents existed.
- Muscarinic blockade partially offsets striatal D2 antagonism, which is why extrapyramidal symptoms are less frequent than with high-potency agents.
- Blockade of hERG potassium channels and of neuronal sodium channels underlies QT prolongation and its comparatively high seizure-threshold reduction.

PHARMACOKINETICS

- Oral bioavailability is erratic at roughly 10-30 percent because of heavy first-pass metabolism; intramuscular dosing gives four to ten times higher exposure.
- Terminal half-life is about 30 hours, but numerous active and inactive metabolites prolong tissue effects well beyond plasma clearance.
- Metabolized principally by CYP2D6 with contributions from CYP1A2 and CYP3A4, followed by sulfoxidation and glucuronide conjugation in the liver.
- It is itself a moderate CYP2D6 inhibitor, raising exposure to substrates such as metoprolol, tricyclic antidepressants, and atomoxetine.
- Highly lipophilic and about 95 percent protein bound, with a large volume of distribution and no meaningful renal clearance of parent drug.

ADVERSE EFFECTS

- Sedation affects the majority of patients early, and orthostatic hypotension is dose-limiting, particularly after the first parenteral doses.
- Anticholinergic burden is high, producing dry mouth, blurred vision, constipation, urinary retention, and delirium risk in older adults.
- Extrapyramidal symptoms occur in roughly 10-20 percent, lower than with haloperidol, but tardive dyskinesia risk still accrues with chronic use.
- Photosensitivity is common and prolonged high-dose therapy can cause blue-gray skin pigmentation plus lens and corneal deposits.
- Cholestatic jaundice occurs in under 1 percent, usually in the first month, and rare agranulocytosis and neuroleptic malignant syndrome are reported.
- It lowers seizure threshold more than most antipsychotics and prolongs the QT interval in a dose-dependent fashion.

MONITORING

- Check supine and standing blood pressure at baseline, after each increase, and before repeat parenteral doses given the alpha-blockade.
- Obtain baseline liver enzymes and repeat if jaundice, pruritus, or malaise appears, since cholestasis clusters in the first four weeks.
- Get a CBC at baseline and whenever fever or sore throat develops; stop the drug for an absolute neutrophil count below 1000 per microliter.
- Perform an AIMS every 6 months and a slit-lamp or ophthalmologic exam periodically for patients on prolonged high-dose therapy.
- ECG at baseline and after dose escalation when QT-prolonging drugs, electrolyte disturbance, or cardiac disease are present.

INTERACTIONS & CAUTIONS

- Epinephrine given for chlorpromazine-induced hypotension can paradoxically lower pressure further; use phenylephrine or norepinephrine instead.
- Additive hypotension with antihypertensives, alpha-blockers, and nitrates, and additive sedation with opioids, benzodiazepines, and alcohol.
- As a CYP2D6 inhibitor it raises levels of metoprolol, tricyclics, and atomoxetine, while CYP1A2 inducers such as smoking lower its own levels.
- Additive QT prolongation with methadone, ondansetron, macrolides, and antiarrhythmics; combined anticholinergics precipitate ileus or delirium.
- Contraindicated with comatose states, severe CNS depression, and known phenothiazine hypersensitivity; avoid in dementia with Lewy bodies.

SPECIAL POPULATIONS

- Pregnancy data are extensive without a clear teratogenic signal, but third-trimester exposure risks neonatal extrapyramidal and withdrawal symptoms.
- Small amounts appear in breast milk; monitor the infant for sedation and poor feeding, and prefer better-studied agents when a choice exists.
- Labeled for children aged 6 months and older; pediatric dosing is **0.55 mg/kg** every 4-6 hours as needed, with lower ceilings than adults.
- In older adults it appears on the Beers criteria for anticholinergic and hypotensive burden; use only briefly and at markedly reduced doses.
- Hepatic impairment substantially raises exposure and jaundice risk, while renal impairment requires no dose change for the parent drug.

☆ PRESCRIBING PEARLS

- Never treat its hypotension with epinephrine; unopposed beta-2 vasodilation worsens the drop.
- Counsel sun protection early; photosensitivity burns appear within days of starting therapy.
- Chlorpromazine **100 mg** is roughly equivalent to haloperidol **2 mg** when converting antipsychotics.

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.