FIRST-GENERATION ANTIPSYCHOTIC

Perphenazine

Trilafon (brand discontinued; generic only)

Mid-potency phenothiazine best known as the first-generation comparator in CATIE, balancing moderate extrapyramidal and metabolic burden.

USUAL ADULT RANGE	HALF-LIFE	METABOLISM	ONSET
8-32 mg/day PO; max 64 mg	~9-12 h; active 7-OH metab	CYP2D6 > 1A2, 3A4	1-2 wks; 4-6 wks full effect

⚠ FDA BOXED WARNING

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

INDICATIONS

- FDA-approved for the treatment of schizophrenia in adults, with dosing ranges separated for outpatients and hospitalized patients.
- FDA-approved for the control of severe nausea and vomiting in adults at doses well below the antipsychotic range.
- Off-label use in acute bipolar mania as an adjunct to lithium or valproate when a first-generation agent is preferred or better tolerated.
- Off-label treatment of psychotic depression, historically as a fixed combination with amitriptyline that is no longer marketed in the United States.
- Performed comparably to olanzapine, quetiapine, and risperidone on all-cause discontinuation in the CATIE trial, supporting its continued use.
- Not indicated for dementia-related psychosis or for nonpsychotic anxiety and insomnia, where safer alternatives exist.

DOSING & TITRATION

- Outpatients typically start at **4-8 mg** orally three times daily, then reduce to the lowest dose that maintains symptom control.
- Hospitalized patients may receive **8-16 mg** two to four times daily; the labeled maximum is **64 mg/day** in total.
- Most stabilized adults do well on **8-32 mg/day** in divided doses, and exceeding 24 mg daily sharply increases extrapyramidal symptoms.
- For severe nausea and vomiting, use **8-16 mg/day** orally in divided doses, with a ceiling of **24 mg/day** for that indication.
- No formal renal adjustment; use lower doses and slower titration in hepatic impairment, and avoid the drug in overt liver disease.
- Taper gradually over several weeks when discontinuing to avoid cholinergic rebound and emergent withdrawal dyskinesias.

MECHANISM OF ACTION

- Dopamine D2 receptor antagonism of intermediate potency, requiring roughly eight to sixteen milligrams daily for antipsychotic D2 occupancy.
- Extrapyramidal liability sits between haloperidol and chlorpromazine because striatal blockade is only partially offset by weak muscarinic effects.
- Moderate histamine H1 and alpha-1 antagonism produce intermediate sedation and orthostatic hypotension relative to other phenothiazines.
- Blockade of D2 receptors in the chemoreceptor trigger zone provides the strong antiemetic effect exploited at subantipsychotic doses.
- Tuberoinfundibular D2 antagonism raises prolactin substantially, a class effect shared with all typical phenothiazines.

PHARMACOKINETICS

- Oral bioavailability is roughly 20-25 percent because of extensive first-pass metabolism, with peak concentrations at 1 to 3 hours.
- Elimination half-life is about 9 to 12 hours, which supports two or three times daily dosing during active treatment.
- CYP2D6 is the main metabolic pathway with contributions from CYP1A2 and CYP3A4; poor metabolizers reach much higher exposures.
- The 7-hydroxyperphenazine metabolite is pharmacologically active and contributes to both efficacy and extrapyramidal effects.
- Protein binding is high and elimination is essentially hepatic, with only trace unchanged drug appearing in the urine.

ADVERSE EFFECTS

- Extrapyramidal symptoms affect roughly 20-30 percent of patients, with akathisia the most common and dose-related manifestation.
- Tardive dyskinesia accumulates with duration of exposure, and in CATIE perphenazine showed rates broadly similar to comparator atypicals.
- Hyperprolactinemia is frequent and symptomatic, producing amenorrhea, galactorrhea, gynecomastia, and sexual dysfunction.
- Sedation, orthostatic hypotension, dry mouth, and constipation are moderate, more than with haloperidol and less than with chlorpromazine.
- Weight gain and metabolic change are modest, one reason perphenazine remains an option for patients with metabolic vulnerability.
- Rare serious events include neuroleptic malignant syndrome, agranulocytosis, cholestatic jaundice, seizures, and QT prolongation.

MONITORING

- Baseline and semiannual AIMS with an interval extrapyramidal exam at each visit, using more frequent screening in older patients.
- Baseline CBC and liver enzymes, with repeat testing prompted by fever, sore throat, jaundice, or unexplained fatigue.
- Blood pressure sitting and standing during titration, since orthostasis is most likely in the first two weeks and after increases.
- Weight, waist, fasting glucose, and lipids at baseline, at 3 months, and annually thereafter, consistent with antipsychotic standards.
- ECG when cardiac disease, electrolyte abnormality, or another QT-prolonging drug is present, and creatine kinase if rigidity develops.

INTERACTIONS & CAUTIONS

- Strong CYP2D6 inhibitors such as paroxetine, fluoxetine, and bupropion raise perphenazine levels several-fold and increase movement effects.
- CYP1A2 and CYP3A4 inducers including carbamazepine, rifampin, and tobacco smoke lower concentrations and may cause relapse.
- Additive sedation with opioids, benzodiazepines, and alcohol; additive anticholinergic load with benztropine and antihistamines.
- Combined QT-prolonging agents warrant ECG monitoring, and antihypertensives compound the alpha-blockade-mediated orthostatic drop.
- Contraindicated in comatose states, severe CNS depression, blood dyscrasias, liver damage, and known phenothiazine hypersensitivity.

SPECIAL POPULATIONS

- Human pregnancy data show no clear teratogenic signal, but late gestational exposure risks neonatal extrapyramidal and withdrawal signs.
- Small amounts enter breast milk; nursing is generally acceptable with monitoring of the infant for sedation and abnormal movements.
- Pediatric safety and efficacy are not established for children under 12, so use in that group is off-label and specialist-directed.
- Older adults require reduced doses because of heightened tardive dyskinesia, orthostasis, and the boxed dementia mortality warning.
- Renal impairment does not require adjustment; hepatic impairment increases exposure and is a labeled caution or contraindication.

PRESCRIBING PEARLS

- CATIE showed perphenazine matched most atypicals on discontinuation at far lower cost and metabolic risk.
- Divide the daily dose; the 9-12 hour half-life makes once-daily oral dosing prone to trough breakthrough.
- Perphenazine **8 mg** approximates haloperidol **2 mg** and chlorpromazine **100 mg** in potency.

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.