PERPHENAZINE

**Brands** • Trilafon
*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine receptor antagonist (D-RAn)
- Conventional antipsychotic (neuroleptic, phenothiazine, dopamine 2 antagonist, antiemetic)

**Commonly Prescribed for**
*bold for FDA approved*
- Schizophrenia
- Nausea, vomiting
- Other psychotic disorders
- Bipolar disorder

**How the Drug Works**
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- Combination of dopamine D2, histamine H1, and cholinergic M1 blockade in the vomiting center may reduce nausea and vomiting

**How Long Until It Works**
- Psychotic symptoms can improve within 1 week, but may take several weeks for full effect on behavior
- Injection: initial effect after 10 minutes, peak after 1–2 hours
- Actions on nausea and vomiting are immediate

**If It Works**
- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Continue treatment in schizophrenia until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis in schizophrenia
- For second and subsequent episodes of psychosis in schizophrenia, treatment may need to be indefinite
- Reduces symptoms of acute psychotic mania but not proven as a mood stabilizer

**Best Augmenting Combos for Partial Response or Treatment Resistance**
- Augmentation of conventional antipsychotics has not been systematically studied
- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially short-term for agitation

**Tests**
- Since conventional antipsychotics are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment

**If It Doesn’t Work**
- Consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine

**Best Augmenting Combos**
- Augmentation of conventional antipsychotics has not been systematically studied
- Addition of a mood-stabilizing anticonvulsant such as valproate, carbamazepine, or lamotrigine may be helpful in both schizophrenia and bipolar mania
- Augmentation with lithium in bipolar mania may be helpful
- Addition of a benzodiazepine, especially short-term for agitation

**Tests**
- Since conventional antipsychotics are frequently associated with weight gain, before starting treatment, weigh all patients and determine if the patient is already overweight (BMI 25.0–29.9) or obese (BMI ≥30)
- Before giving a drug that can cause weight gain to an overweight or obese patient, consider determining whether the patient already has pre-diabetes (fasting plasma glucose 100–125 mg/dL), diabetes (fasting plasma glucose >126 mg/dL), or dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol), and treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management
- Monitor weight and BMI during treatment
Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics.

While giving a drug to a patient who has gained >5% of initial weight, consider evaluating for the presence of pre-diabetes, diabetes, or dyslipidemia, or consider switching to a different antipsychotic.

- Should check blood pressure in the elderly before starting and for the first few weeks of treatment.
- Monitoring elevated prolactin levels of dubious clinical benefit.
- Phenothiazines may cause false-positive phenylketonuria results.
- Patients with low white blood cell count (WBC) or history of drug-induced leucopenia/neutropenia should have complete blood count (CBC) monitored frequently during the first few months and perphenazine should be discontinued at the first sign of decline of WBC in the absence of other causative factors.

Life-Threatening or Dangerous Side Effects

- Rare neuroleptic malignant syndrome.
- Rare jaundice, agranulocytosis.
- Rare seizures.
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis.

Weight Gain

- Many experience and/or can be significant in amount.

Sedation

- Many experience and/or can be significant in amount.
- Sedation is usually transient.

What to Do About Side Effects

- Wait.
- Wait.
- Wait.
- For motor symptoms, add an anticholinergic agent.
- Reduce the dose.
- For sedation, give at night.
- Switch to an atypical antipsychotic.
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia.

Best Augmenting Agents for Side Effects

- Benztropine or trihexyphenidyl for motor side effects.
- Sometimes amantadine can be helpful for motor side effects.

SIDE EFFECTS

How Drug Causes Side Effects

- By blocking dopamine 2 receptors in the striatum, it can cause motor side effects.
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin.
- By blocking dopamine 2 receptors excessively in the mesocortical and mesolimbic dopamine pathways, especially at high doses, it can cause worsening of negative and cognitive symptoms (neuroleptic-induced deficit syndrome).
- Anticholinergic actions may cause sedation, blurred vision, constipation, dry mouth.
- Antihistaminic actions may cause sedation, weight gain.
- By blocking alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension.
- Mechanism of weight gain and any possible increased incidence of diabetes or dyslipidemia with conventional antipsychotics is unknown.

Notable Side Effects

- Neuroleptic-induced deficit syndrome.

- Akathisia.
- Extrapyramidal symptoms, parkinsonism, tardive dyskinesia.
- Galactorrhea, amenorrhea.
  - Dizziness, sedation.
  - Dry mouth, constipation, urinary retention, blurred vision.
  - Decreased sweating.
  - Sexual dysfunction.
  - Hypotension, tachycardia, syncope.
  - Weight gain.

- Life-Threatening or Dangerous Side Effects:
  - Rare neuroleptic malignant syndrome.
  - Rare jaundice, agranulocytosis.
  - Rare seizures.
  - Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis.

- Weight Gain:
  - Many experience and/or can be significant in amount.
- Sedation:
  - Many experience and/or can be significant in amount.
  - Sedation is usually transient.

- What to Do About Side Effects:
  - Wait.
  - Wait.
  - Wait.
  - For motor symptoms, add an anticholinergic agent.
  - Reduce the dose.
  - For sedation, give at night.
  - Switch to an atypical antipsychotic.
  - Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia.

- Best Augmenting Agents for Side Effects:
  - Benztropine or trihexyphenidyl for motor side effects.
  - Sometimes amantadine can be helpful for motor side effects.
• Benzodiazepines may be helpful for akathisia
• Many side effects cannot be improved with an augmenting agent

### DOSING AND USE

#### Usual Dosage Range
- Psychosis: oral: 12–24 mg/day; 16–64 mg/day in hospitalized patients
- Nausea/vomiting: 8–16 mg/day oral, 5 mg intramuscularly

#### Dosage Forms
- Tablet 2 mg, 4 mg, 8 mg, 16 mg
- Injection 5 mg/mL

#### How to Dose
- Oral: psychosis: 4–8 mg 3 times a day; 8–16 mg 2 times a day to 4 times a day in hospitalized patients; maximum 64 mg/day
- Oral: nausea/vomiting: 8–16 mg/day in divided doses; maximum 24 mg/day
- Intramuscular: psychosis: initial 5 mg; can repeat every 6 hours; maximum 15 mg/day (30 mg/day in hospitalized patients)

#### Dosing Tips
- Injection contains sulfites that may cause allergic reactions, particularly in patients with asthma
- Oral perphenazine is less potent than the injection, so patients should receive equal or higher dosage when switched from injection to tablet
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

#### Overdose
- Extrapyramidal symptoms, coma, hypotension, sedation, seizures, respiratory depression

#### Long-Term Use
- Some side effects may be irreversible (e.g., tardive dyskinesia)

#### Habit Forming
- No

#### How to Stop
- Slow down-titration of oral formulation (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid oral discontinuation may lead to rebound psychosis and worsening of symptoms
- If antiparkinson agents are being used, they should be continued for a few weeks after perphenazine is discontinued

### Pharmacokinetics
- Half-life approximately 9.5 hours

#### Drug Interactions
- May decrease the effects of levodopa, dopamine agonists
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions perphenazine may antagonize
- Additive effects may occur if used with CNS depressants
- Anticholinergic effects may occur if used with atropine or related compounds
- Some patients taking a neuroleptic and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome
- Epinephrine may lower blood pressure; diuretics and alcohol may increase risk of hypotension

#### Other Warnings/Precautions
- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use cautiously in patients with respiratory disorders
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- Do not use epinephrine in event of overdose as interaction with some pressor agents may lower blood pressure
- Avoid undue exposure to sunlight
- Avoid extreme heat exposure
- Use with caution in patients with respiratory disorders, glaucoma, or urinary retention
- Antiemetic effect of perphenazine may mask signs of other disorders or overdose;
suppression of cough reflex may cause asphyxia
• Observe for signs of ocular toxicity (corneal and lenticular deposits)
• Use only with caution if at all in Parkinson’s disease or Lewy body dementia

Do Not Use
• If patient is in a comatose state or has CNS depression
• If there is the presence of blood dyscrasias, subcortical brain damage, bone marrow depression, or liver disease
• If there is a proven allergy to perphenazine
• If there is a known sensitivity to any phenothiazine

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• There is a risk of abnormal muscle movements and withdrawal symptoms in newborns whose mothers took an antipsychotic during the third trimester; symptoms may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty feeding
• Reports of extrapyramidal symptoms, jaundice, hyperreflexia, hyporeflexia in infants whose mothers took a phenothiazine during pregnancy
• Perphenazine should only be used during pregnancy if clearly needed
• Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
• Atypical antipsychotics may be preferable to conventional antipsychotics or anticonvulsant mood stabilizers if treatment is required during pregnancy

Breast Feeding
• Unknown if perphenazine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk

THE ART OF PSYCHOPHARMACOLOGY
Potential Advantages
• Intramuscular formulation for emergency use

Potential Disadvantages
• Patients with tardive dyskinesia
• Children
• Elderly

Children and Adolescents
• Not recommended for use in children under age 12
• Over age 12: if given intramuscularly, should receive lowest adult dose
• Generally consider second-line after atypical antipsychotics
Primary Target Symptoms

- Positive symptoms of psychosis
- Motor and autonomic hyperactivity
- Violent or aggressive behavior

Pearls

- Recent landmark head-to-head study in schizophrenia suggests comparable effectiveness with some atypical antipsychotics
- Perphenazine is a higher potency phenothiazine
- Less risk of sedation and orthostatic hypotension but greater risk of extrapyramidal symptoms than with low potency phenothiazines
- Patients have very similar antipsychotic responses to any conventional antipsychotic, which is different from atypical antipsychotics where antipsychotic responses of individual patients can occasionally vary greatly from one atypical antipsychotic to another
- Patients with inadequate responses to atypical antipsychotics may benefit from a trial of augmentation with a conventional antipsychotic such as perphenazine or from switching to a conventional antipsychotic such as perphenazine

- However, long-term polypharmacy with a combination of a conventional antipsychotic such as perphenazine with an atypical antipsychotic may combine their side effects without clearly augmenting the efficacy of either
- For treatment-resistant patients, especially those with impulsivity, aggression, violence, and self-harm, long-term polypharmacy with 2 atypical antipsychotics or with 1 atypical antipsychotic and 1 conventional antipsychotic may be useful or even necessary while closely monitoring
- In such cases, it may be beneficial to combine 1 depot antipsychotic with 1 oral antipsychotic
- Although a frequent practice by some prescribers, adding 2 conventional antipsychotics together has little rationale and may reduce tolerability without clearly enhancing efficacy
- Availability of alternative treatments and risk of tardive dyskinesia make utilization of perphenazine for nausea and vomiting a short-term and second-line treatment option

Suggested Reading


