HALOPERIDOL

**Therapeutics**

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

**Generic?**  Yes

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

**Commonly Prescribed for** *(bold for FDA approved)*
• Manifestations of psychotic disorders (oral, immediate-release injection)
• Tics and vocal utterances in Tourette’s syndrome (oral, immediate-release injection)
• Second-line treatment of severe behavior problems in children of combative, explosive hyperexcitability (oral, immediate-release injection)
• Second-line short-term treatment of hyperactive children (oral, immediate-release injection)
• Treatment of schizophrenic patients who require prolonged parenteral antipsychotic therapy (depot intramuscular decanoate)
• Bipolar disorder
• Behavioral disturbances in dementias
• Delirium (with lorazepam)

**How the Drug Works**
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and possibly combative, explosive, and hyperactive behaviors
• Blocks dopamine 2 receptors in the nigrostriatal pathway, improving tics and other symptoms in Tourette’s syndrome

**How Long Until It Works**
• Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior

**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 or as an effective maintenance treatment in bipolar disorder
• After reducing acute psychotic symptoms in mania, switch to a mood stabilizer and/or an atypical antipsychotic for mood stabilization and maintenance

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

**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
* 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
• 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 haloperidol should be discontinued at the first sign of decline of WBC in the absence of other causative factors

Notable Side Effects

* Neuroleptic-induced deficit syndrome
* Akathisia
* Extrapyramidal symptoms, parkinsonism, tardive dyskinesia, tardive dystonia
* Galactorrhea, amenorrhea
  • Dizziness, sedation
  • Dry mouth, constipation, urinary retention, blurred vision
  • Decreased sweating
  • Hypotension, tachycardia, hypertension
  • Weight gain

Life-Threatening or Dangerous Side Effects

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

Weight Gain

• Occurs in significant minority

Sedation

• 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
- 1–40 mg/day orally
- Immediate-release injection 2–5 mg each dose
- Decanoate injection 10–20 times the previous daily dose of oral antipsychotic (see Haloperidol Decanoate section after Pearls for dosing and use)

Dosage Forms
- Tablet 0.5 mg scored, 1 mg scored, 2 mg scored, 5 mg scored, 10 mg scored, 20 mg scored
- Concentrate 2 mg/mL
- Solution 1 mg/mL
- Injection 5 mg/mL (immediate-release)
- Decanoate injection 50 mg/mL, 100 mg/mL

How to Dose
- Oral: initial 1–15 mg/day; can give once daily or in divided doses at the beginning of treatment during rapid dose escalation; increase as needed; can be dosed up to 100 mg/day; safety not established for doses over 100 mg/day
- Immediate-release injection: initial dose 2–5 mg; subsequent doses may be given as often as every hour; patient should be switched to oral administration as soon as possible

Dosing Tips – Oral
- Haloperidol is frequently dosed too high
- Some studies suggest that patients who respond well to low doses of haloperidol (e.g., approximately 2 mg/day) may have efficacy similar to atypical antipsychotics for both positive and negative symptoms of schizophrenia
- Higher doses may actually induce or worsen negative symptoms of schizophrenia
- Low doses, however, may not have beneficial actions for treatment-resistant cases or violence
- One of the only antipsychotics with a depot formulation lasting for up to a month
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose
- Fatalities have been reported; extrapyramidal symptoms, hypotension, sedation, respiratory depression, shock-like state

Long-Term Use
- Often used for long-term maintenance
- 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 haloperidol is discontinued

Pharmacokinetics
- Decanoate half-life approximately 3 weeks
- Oral half-life approximately 12–38 hours

Drug Interactions
- May decrease the effects of levodopa, dopamine agonists
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions haloperidol may antagonize
- Additive effects may occur if used with CNS depressants; dose of other agent should be reduced
- Some pressor agents (e.g., epinephrine) may interact with haloperidol to lower blood pressure
- Haloperidol and anticholinergic agents together may increase intraocular pressure
- Reduces effects of anticoagulants
- Plasma levels of haloperidol may be lowered by rifampin
- Some patients taking haloperidol and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome
haloperidol (continued)

- May enhance effects of antihypertensive drugs

**Other Warnings/ Precautions**

- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use with caution in patients with respiratory disorders
- Avoid extreme heat exposure
- If haloperidol is used to treat mania, patients may experience a rapid switch to depression
- Patients with thyrotoxicosis may experience neurotoxicity
- Use only with caution if at all in Parkinson’s disease or Lewy body dementia
- Higher doses and IV administration may be associated with increased risk of QT prolongation and torsades de pointes; use particular caution if patient has a QT-prolonging condition, underlying cardiac abnormalities, hypothyroidism, familial long-QT syndrome, or is taking a drug known to prolong QT interval

**Do Not Use**

- If patient is in comatose state or has CNS depression
- If patient has Parkinson’s disease
- If there is a proven allergy to haloperidol

**SPECIAL POPULATIONS**

**Renal Impairment**

- Use with caution

**Hepatic Impairment**

- Use with caution

**Cardiac Impairment**

- Use with caution because of risk of orthostatic hypertension
- Possible increased risk of QT prolongation or torsades de pointes at higher doses or with IV administration

**Elderly**

- Lower doses should be used and patient should be monitored closely
- Elderly patients may be more susceptible to respiratory side effects and hypotension

- Although conventional antipsychotics are commonly used for behavioral disturbances in dementia, no agent has been approved for treatment of elderly patients with dementia-related psychosis
- Elderly patients with dementia-related psychosis treated with antipsychotics are at an increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

**Children and Adolescents**

- Safety and efficacy have not been established; not intended for use under age 3
- Oral: initial 0.5 mg/day; target dose 0.05–0.15 mg/kg per day for psychotic disorders; 0.05–0.075 mg/kg per day for nonpsychotic disorders
- Generally consider second-line after atypical antipsychotics

**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 conventional antipsychotic during pregnancy
- Reports of limb deformity in infants whose mothers took haloperidol during pregnancy
- Haloperidol should generally not be used during the first trimester

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Haloperidol 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
Some drug is found in mother’s breast milk
Recommended either to discontinue drug or bottle feed

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Intramuscular formulation for emergency use
• 4-week depot formulation for noncompliance
• Low-dose responders may have comparable positive and negative symptom efficacy to atypical antipsychotics
• Low-cost, effective treatment

Potential Disadvantages
• Patients with tardive dyskinesia or who wish to avoid tardive dyskinesia and extrapyramidal symptoms
• Vulnerable populations such as children or elderly
• Patients with notable cognitive or mood symptoms

Primary Target Symptoms
• Positive symptoms of psychosis
• Violent or aggressive behavior

Pearls
• Prior to the introduction of atypical antipsychotics, haloperidol was one of the most preferred antipsychotics
• Haloperidol may still be a useful antipsychotic, especially at low doses for those patients who require management with a conventional antipsychotic or who cannot afford an atypical antipsychotic
• Low doses may not induce negative symptoms, but high doses may
• Not clearly effective for improving cognitive or affective symptoms of schizophrenia

• May be effective for bipolar maintenance, but there may be more tardive dyskinesia when affective disorders are treated with a conventional antipsychotic long-term
• Less sedating than many other conventional antipsychotics, especially “low potency” phenothiazines
• Haloperidol is often used to treat delirium, generally in combination with lorazepam, with the haloperidol dose 2 times the lorazepam dose
• Haloperidol’s long-acting intramuscular formulation lasts up to 4 weeks, whereas some other long-acting intramuscular antipsychotics may last only up to 2 weeks
• Decanoate administration is intended for patients with chronic schizophrenia who have been stabilized on oral antipsychotic medication
• 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 receiving atypical antipsychotics may occasionally require a “top up” of a conventional antipsychotic such as haloperidol to control aggression or violent behavior
• Patients with inadequate responses to atypical antipsychotics may benefit from a trial of augmentation with a conventional antipsychotic such as haloperidol or from switching to a conventional antipsychotic such as haloperidol
• However, long-term polypharmacy with a combination of a conventional antipsychotic such as haloperidol 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
HALOPERIDOL (continued)

<table>
<thead>
<tr>
<th>Haloperidol Decanoate Properties</th>
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<tbody>
<tr>
<td>Vehicle</td>
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<tr>
<td>T&lt;sub&gt;max&lt;/sub&gt; with multiple dosing</td>
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<td>Time to reach steady state</td>
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<tr>
<td>Dosage forms</td>
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<tr>
<td>Injection volume</td>
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**Usual Dosage Range**
- 10–20 times the previous oral dose

**How to Dose**
- Conversion from oral: loading with 20 times the oral daily dose (mg/day) for the first month, divided into 2 biweekly injections; weekly loading is an alternate option; may require oral coverage for the first week

**Dosing Tips**
- With LAIs, the absorption rate constant is slower than the elimination rate constant, thus resulting in “flip-flop” kinetics—i.e., time to steady-state is a function of absorption rate, while concentration at steady-state is a function of elimination rate
- The rate-limiting step for plasma drug levels for LAIs is not drug metabolism, but rather slow absorption from the injection site
- In general, 5 half-lives of any medication are needed to achieve 97% of steady-state levels
- The long half-lives of depot antipsychotics mean that one must either adequately load the dose (if possible) or provide oral supplementation
- The failure to adequately load the dose leads either to prolonged cross-titration from oral antipsychotic or to subtherapeutic antipsychotic plasma levels for weeks or months in patients who are not receiving (or adhering to) oral supplementation
- Because plasma antipsychotic levels increase gradually over time, dose requirements may ultimately decrease from initial; obtaining periodic plasma levels can be beneficial to prevent unnecessary plasma level creep
- The time to get a blood level for patients receiving LAI is the morning of the day they will receive their next injection
- Advantages: reliable conversion formula from oral dosing, established loading regimens
- Disadvantages: higher incidence of local site reactions (due to sesame oil vehicle); even with loading, may require oral coverage for at least a week
- Response threshold is generally 3–5 ng/mL; plasma levels greater than 20 ng/mL are generally not well tolerated
- Single injection volumes greater than 300 (3 mL) are not tolerated, so patients who require higher doses typically receive the monthly dose as split injections every 2 weeks
- A loading strategy advocated by some is to give 300 mg LAI every 1–2 weeks for 2 doses and then measure plasma drug concentrations just prior to a third loading dose to see if a third dose is necessary
• Discontinuation of oral antipsychotic can begin immediately if adequate loading is pursued; however, oral coverage may still be necessary for the first week
• How to discontinue oral formulations
  • Down-titration is not required for: amisulpride, aripiprazole, brexpiprazole, cariprazine, paliperidone ER
  • 1-week down-titration is required for: iloperidone, lurasidone, risperidone, ziprasidone
  • 3–4-week down-titration is required for: asenapine, olanzapine, quetiapine
  • 4+-week down-titration is required for: clozapine
• For patients taking benzodiazepine or anticholinergic medication, this can be continued during cross-titration to help alleviate side effects such as insomnia, agitation, and/or psychosis. Once the patient is stable on LAI, these can be tapered one at a time as appropriate.

Suggested Reading


