FLUPHENAZINE

**THERAPEUTICS**

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

**Generic?** Yes

**Class**  
• Conventional antipsychotic (neuroleptic, phenothiazine, dopamine 2 antagonist)

**Commonly Prescribed for**  
(bold for FDA approved)  
• Psychotic disorders  
• Bipolar disorder

**How the Drug Works**  
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis

**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, amisulpride, asenapine, iloperidone, lurasidone)  
• 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
• 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 fluphenazine should be discontinued at the first sign of decline of WBC in the absence of other causative factors

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

**DOSING AND USE**

**Usual Dosage Range**
- Oral: 1–20 mg/day maintenance
- Intramuscular: generally 1/3 to 1/2 the oral dose
- Decanoate for intramuscular or subcutaneous administration: 12.5–100 mg/2 weeks maintenance (see Fluphenazine Decanoate section after Pearls for dosing and use)
**Dosage Forms**
- Tablet 1 mg, 2.5 mg scored, 5 mg scored, 10 mg scored
- Decanoate for long-acting intramuscular or subcutaneous administration 25 mg/mL
- Injection for acute intramuscular administration 2.5 mg/mL
- Elixir 2.5 mg/5 mL
- Concentrate 5 mg/mL

**How to Dose**
- Oral: initial 0.5–10 mg/day in divided doses; maximum 40 mg/day
- Intramuscular (short-acting): initial 1.25 mg; 2.5–10 mg/day can be given in divided doses every 6–8 hours; maximum dose generally 10 mg/day

**Dosing Tips – Oral**
- Patients receiving atypical antipsychotics may occasionally require a “top up” of a conventional antipsychotic to control aggression or violent behavior
- Fluphenazine tablets 2.5 mg, 5 mg, and 10 mg contain tartrazine, which can cause allergic reactions, especially in patients sensitive to aspirin
- Oral solution should not be mixed with drinks containing caffeine, tannic acid (tea), or pectinates (apple juice)
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

**Pharmacokinetics**
- Mean half-life of oral formulation approximately 15 hours
- Mean half-life of intramuscular formulation approximately 6.8–9.6 days

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

**Other Warnings/Precautions**
- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- Avoid undue exposure to sunlight
- Use cautiously in patients with respiratory disorders
- Avoid extreme heat exposure
- Antiemetic effect can mask signs of other disorders or overdose
- Do not use epinephrine in event of overdose as interaction with some pressor agents may lower blood pressure
- Use only with caution if at all in Parkinson’s disease or Lewy body dementia

**How to Stop**
- Slow down-titration of oral formulation (over 6 to 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 fluphenazine is discontinued

**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

**Do Not Use**
- If patient is in a comatose state or has CNS depression
- If patient is taking cabergoline, pergolide, or metrizamide
- If there is a proven allergy to fluphenazine
- If there is a known sensitivity to any phenothiazine
FLUPHENAZINE (continued)

**SPECIAL POPULATIONS**

**Renal Impairment**
- Use with caution; titration should be slower

**Hepatic Impairment**
- Use with caution; titration should be slower

**Cardiac Impairment**
- Cardiovascular toxicity can occur, especially orthostatic hypotension

**Elderly**
- Titration should be slower; lower initial dose (1–2.5 mg/day)
- Elderly patients may be more susceptible to adverse effects
- 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 not established
- Decanoate and enanthate injectable formulations are contraindicated in children under age 12
- 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 (PLLDR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- 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
- Fluphenazine should only be used during pregnancy if clearly indicated
- 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
- Effects on infant have been observed (dystonia, tardive dyskinesia, sedation)
- Recommended either to discontinue drug or bottle feed

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**
- Intramuscular formulation for (emergency use
- Relatively rapid onset of LAI (but see fluphenazine decanoate after Pearls section)

**Potential Disadvantages**
- Patients with tardive dyskinesia
- Children
- Elderly

**Primary Target Symptoms**
- Positive symptoms of psychosis
- Motor and autonomic hyperactivity
- Violent or aggressive behavior

**Pearls**
- Fluphenazine is a high-potency phenothiazine
- Less risk of sedation and orthostatic hypotension but greater risk of extrapyramidal symptoms than with low potency phenothiazines
• Not shown to be effective for behavioral problems in mental retardation
• 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 fluphenazine or from switching to a conventional antipsychotic such as fluphenazine
• However, long-term polypharmacy with a combination of a conventional antipsychotic such as fluphenazine 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

### Usual Dosage Range
• 12.5–100 mg/2 weeks maintenance

### How to Dose
• Conversion from oral: can either supplement with oral formulation at half-dose for at least 2 weeks OR use weekly loading injections of 1.6 times the oral daily dose (mg/day) for 4–6 weeks

### 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
• 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 sub-therapeutic 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: Early peak (see following graph) may be beneficial in the management of acute patients
• Disadvantages: Early peak also carries risk of EPS or akathisia in first 48 hours; 2-week injection schedule; higher incidence of local site reactions (due to sesame oil vehicle)
• Response threshold is 0.81 ng/mL; plasma levels greater than 2–3 ng/mL are generally not well tolerated

### Fluphenazine Decanoate

<table>
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<tr>
<th>Vehicle</th>
<th>Sesame Oil</th>
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<tr>
<td>Tmax</td>
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<tr>
<td>Able to be loaded</td>
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<tr>
<td>Time to reach steady state</td>
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<td>Dosing schedule (maintenance)</td>
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SWITCHING FROM ORAL ANTIPSYCHOTICS TO FLUPHENAZINE DECANOATE

Fluphenazine Decanoate Single-Dose (25 mg) Kinetics

- Discontinuation of oral antipsychotic can begin immediately if adequate loading is pursued; otherwise, supplement with oral formulation at half-dose for at least 2 weeks
- How to discontinue oral formulations
  - Down-titration is not required for: amisulpride, aripiprazole, brexiprazole, 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


