FLUPENTHIXOL

THERAPEUTICS

Brands • Depixol
see index for additional brand names

Generic? No

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

Commonly Prescribed for (bold for FDA approved)
• Schizophrenia
• Depression (low dose)
• Other psychotic disorders
• Bipolar disorder

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

How Long Until It Works
• With injection, psychotic symptoms can improve within a few days, but it may take 1–2 weeks for notable improvement
• With oral formulation, 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)
• 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,
**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 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
- Extrapyramidal symptoms (more common at start of treatment), parkinsonism
- Insomnia, restlessness, agitation, sedation
- Tardive dyskinesia (risk increases with duration of treatment and with dose)
- Galactorrhea, amenorrhea
- Tachycardia
- Weight gain
- Hypomania
- Rare eosinophilia

**Life-Threatening or Dangerous Side Effects**

- Rare neuroleptic malignant syndrome
- Rare seizures
- Rare jaundice, leucopenia
- 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**

- Occurs in significant minority.

**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**

- Oral 3–6 mg/day in divided doses.
- Intramuscular 40–120 mg every 1–4 weeks.

**Dosage Forms**

- Tablet 0.5 mg, 3 mg.
- Injection 20 mg/mL, 100 mg/mL.
**How to Dose**

- **Oral:** initial 1 mg 3 times a day; increase by 1 mg every 2–3 days; maximum generally 18 mg/day
- **Intramuscular:** initial dose 20 mg for patients who have not been exposed to long-acting depot antipsychotics, 40 mg for patients who have previously demonstrated tolerance to long-acting depot antipsychotics; after 4–10 days can give additional 20 mg dose; maximum 200 mg every 1–4 weeks

**Dosing Tips**

- The peak of action for the decanoate is usually 7–10 days, and doses generally have to be administered every 2–3 weeks
- May have more activating effects at low doses, which can sometimes be useful as a second-line, short-term treatment of depression
- Some evidence that flupenthixol may improve anxiety and depression at low doses
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

**Overdose**

- Agitation, confusion, sedation, extrapyramidal symptoms, respiratory collapse, circulatory collapse

**Long-Term Use**

- Safe

**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 flupenthixol is discontinued

**Pharmacokinetics**

- Oral: maximum plasma concentrations within 3–8 hours

- Intramuscular: rate-limiting half-life approximately 8 days with single dose, approximately 17 days with multiple doses

**Drug Interactions**

- May decrease the effects of levodopa, dopamine agonists
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions flupenthixol may antagonize
- CNS effects may be increased if used with other CNS depressants
- Combined use with epinephrine may lower blood pressure
- Ritonavir may increase plasma levels of flupenthixol
- May increase carbamazepine plasma levels
- Some patients taking a neuroleptic and lithium have developed an encephalopathic syndrome similar to neuroleptic malignant syndrome

**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
- In epileptic patients, dose 10–20 mg every 15 days for intramuscular formulation
- Use with caution if at all in patients with Parkinson’s disease, severe arteriosclerosis, or Lewy body dementia
- Possible antiemetic effect of flupenthixol may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia
- Avoid extreme heat exposure
- Do not use epinephrine in event of overdose as interaction with some pressor agents may lower blood pressure

**Do Not Use**

- If patient is taking a large concomitant dose of a sedative hypnotic
- If patient has CNS depression
- If patient is comatose or if there is brain damage
- If there is blood dyscrasia
- If patient has pheochromocytoma
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.

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

**SPECIAL POPULATIONS**

**Renal Impairment**

- Oral: recommended to take half or less of usual adult dose
- Intramuscular: recommended dose schedule generally 10–20 mg every 15 days

**Hepatic Impairment**

- Use with caution
- Oral: recommended to take half or less of usual adult dose

**Cardiac Impairment**

- Use with caution
- Oral: recommended to take half or less of usual adult dose

**Elderly**

- Intramuscular: recommended initial dose generally 5 mg; recommended dose schedule generally 10–20 mg every 15 days
- Oral: recommended to take half or less of usual adult dose
- 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 increased risk of death compared to placebo, and also have an increased risk of cerebrovascular events

**Children and Adolescents**

- Not recommended for use in children

**Pregnancy**

- Not recommended for use during pregnancy

**THE ART OF PSYCHOPHARMACOLOGY**

**Potential Advantages**

- Noncompliant patients

**Potential Disadvantages**

- Children
- Elderly
- Patients with tardive dyskinesia

**Primary Target Symptoms**

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Aggressive symptoms

**Pearls**

- Less sedation and orthostatic hypotension but more extrapyramidal symptoms than some other conventional antipsychotics
- 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 flupenthixol or from switching to a conventional antipsychotic such as flupenthixol.
- However, long-term polypharmacy with a combination of a conventional antipsychotic such as flupenthixol 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.

Suggested Reading

