**ZUCLOPENTHIXOL**

**THERAPEUTICS**

**Brands**
- Clopixol
- Clopixol-Acuphase

*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*
- Acute schizophrenia (oral, acetate injection)
- Maintenance treatment of schizophrenia (oral, decanoate injection)
- Bipolar disorder
- Aggression

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

**How Long Until It Works**
- For injection, psychotic symptoms can improve within a few days, but it may take 1–2 weeks for notable improvement
- For oral formulation, psychotic symptoms can improve within 1 week, but 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
- 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 zuclopenthixol 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**
- Extrapyramidal symptoms
- Tardive dyskinesia (risk increases with duration of treatment and with dose)
- Priapism
- Galactorrhea, amenorrhea
- Rare lens opacity
- Sedation, dizziness
- Dry mouth, constipation, vision problems
- Hypotension
- Weight gain

**Life-Threatening or Dangerous Side Effects**
- Rare neuroleptic malignant syndrome
- Rare neutropenia
- Rare respiratory depression
- Rare 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
- Some people may lose weight

**Sedation**
- Many experience and/or can be significant in amount
- Acetate formulation may be associated with an initial sedative response

**What to Do About Side Effects**
- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Reduce the dose
- For sedation, take 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**
- Benzotropine 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 20–60 mg/day
- Acetate 50–150 mg every 2–3 days
- Decanoate 150–300 mg every 2–4 weeks

Dosage Forms
- Tablet 10 mg, 25 mg, 40 mg
- Acetate 50 mg/mL (equivalent to zuclopenthixol 45.25 mg/mL), 100 mg/2 mL (equivalent to zuclopenthixol 45.25 mg/mL)
- Decanoate 200 mg/mL (equivalent to zuclopenthixol 144.4 mg/mL), 500 mg/mL (equivalent to zuclopenthixol 361.1 mg/mL)

How to Dose
- Oral: initial 10–15 mg/day in divided doses; can increase by 10–20 mg/day every 2–3 days; maintenance dose can be administered as a single nighttime dose; maximum dose generally 100 mg/day
- Injection should be administered intramuscularly in the gluteal region in the morning
- Acetate generally should be administered every 2–3 days; some patients may require a second dose 24–48 hours after the first injection; duration of treatment should not exceed 2 weeks; maximum cumulative dosage should not exceed 400 mg; maximum number of injections should not exceed 4
- Decanoate: initial dose 100 mg; after 1–4 weeks administer a second injection of 100–200 mg; maintenance treatment is generally 100–600 mg every 1–4 weeks

Dosing Tips
- Onset of action of the intramuscular acetate formulation following a single injection is generally 2–4 hours; duration of action is generally 2–3 days
- Zuclopenthixol acetate is not intended for long-term use, and should not generally be used for longer than 2 weeks; patients requiring treatment longer than 2 weeks should be switched to a depot or oral formulation of zuclopenthixol or another antipsychotic
- When changing from zuclopenthixol acetate to maintenance treatment with zuclopenthixol decanoate, administer the last injection of acetate concomitantly with the initial injection of decanoate
- The peak of action for the decanoate is usually 4–9 days, and doses generally have to be administered every 2–3 weeks
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose
- Sedation, convulsions, extrapyramidal symptoms, coma, hypotension, shock, hypo/hyperthermia

Long-Term Use
- Zuclopenthixol decanoate is intended for maintenance treatment
- 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 zuclopenthixol is discontinued

Pharmacokinetics
- Metabolized by CYP450 2D6 and CYP450 3A4
- For oral formulation, elimination half-life approximately 20 hours
- For acetate, rate-limiting half-life approximately 32 hours
- For decanoate, rate-limiting half-life approximately 17–21 days with multiple doses

Drug Interactions
- Theoretically, concomitant use with CYP450 2D6 inhibitors (such as paroxetine and fluoxetine) or with CYP450 3A4 inhibitors (such as fluoxetine and ketoconazole) could raise zuclopenthixol plasma levels and require dosage reduction
Theoretically, concomitant use with CYP450 3A4 inducers (such as carbamazepine) could lower zuclopenthixol plasma levels and require dosage increase.

- CNS effects may be increased if used with other CNS depressants.
- If used with anticholinergic agents, may potentiate their effects.
- Combined use with epinephrine may lower blood pressure.
- Zuclopenthixol may block the antihypertensive effects of drugs such as guanethidine, but may enhance the actions of other antihypertensive drugs.
- Using zuclopenthixol with metoclopramide or piperazine may increase the risk of extrapyramidal symptoms.
- Zuclopenthixol may antagonize the effects of levodopa and dopamine agonists.
- 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 with caution in patients with epilepsy, glaucoma, urinary retention.
- Decanoate should not be used with clozapine because it cannot be withdrawn quickly in the event of serious adverse effects such as neutropenia.
- Possible antiemetic effect of zuclopenthixol may mask signs of other disorders or overdose; suppression of cough reflex may cause asphyxia.
- Use only with great caution if at all in Parkinson's disease or Lewy body dementia.
- Observe for signs of ocular toxicity (pigmentary retinopathy and lenticular and corneal deposits).
- Avoid undue exposure to sunlight.
- 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 is taking guanethidine or a similar acting compound.
- If patient has CNS depression, is comatose, or has subcortical brain damage.
- If patient has acute alcohol, barbiturate, or opiate intoxication.
- If patient has angle-closure glaucoma.
- If patient has pheochromocytoma, circulatory collapse, or blood dyscrasias.
- In case of pregnancy.
- If there is a proven allergy to zuclopenthixol.

SPECIAL POPULATIONS

Renal Impairment
- Use with caution.

Hepatic Impairment
- Use with caution.

Cardiac Impairment
- Use with caution.

Elderly

- Some patients may tolerate lower doses better.
- Maximum acetate dose 100 mg.
- 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 in children under age 18.
- Preliminary open-label data show that oral zuclopenthixol may be effective in reducing aggression in mentally impaired children.

Pregnancy

- Not recommended for use during pregnancy.

If there is a proven allergy to zuclopenthixol.
• 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
• 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
• Infants of women who choose to breast feed should be monitored for possible adverse effects

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages
• Noncompliant patients (decanoate)
• Emergency use (acute injection)

Potential Disadvantages
• Children
• Elderly
• Patients with tardive dyskinesia

Primary Target Symptoms
• Positive symptoms of psychosis
• Negative symptoms of psychosis
• Aggressive symptoms

Pearls
• Zuclopenthixol depot may reduce risk of relapse more than some other depot conventional antipsychotics, but it may also be associated with more adverse effects
• Can combine acute injection with depot injection in the same syringe for rapid onset and long duration effects when initiating treatment
• Zuclopenthixol may have serotonin 2A antagonist properties, but these have never been systematically investigated for atypical antipsychotic properties at low doses
• 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 zuclopenthixol or from switching to a conventional antipsychotic such as zuclopenthixol
• However, long-term polypharmacy with a combination of a conventional antipsychotic such as zuclopenthixol 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


