

## THERAPEUTICS

**Brands** • Tercian

see index for additional brand names

**Generic?** Not in the USA



### Class

- Conventional antipsychotic (neuroleptic, phenothiazine, dopamine 2 antagonist, serotonin dopamine antagonist)

### Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia
- \* Anxiety associated with psychosis (short-term)
- Anxiety associated with nonpsychotic disorders, including mood disorders and personality disorders (short-term)
- Severe depression
- Bipolar disorder
- Other psychotic disorders
- Acute agitation/aggression (injection)
- Benzodiazepine withdrawal



### How the Drug Works

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- \* Although classified as a conventional antipsychotic, cyamemazine is a potent serotonin 2A antagonist
- Affinity at a myriad of other neurotransmitter receptors may contribute to cyamemazine's efficacy
- \* Specifically, antagonist actions at 5HT<sub>2C</sub> receptors may contribute to notable anxiolytic effects in many patients
- 5HT<sub>2C</sub> antagonist actions may also contribute to antidepressant actions in severe depression and to improvement of cognitive and negative symptoms of schizophrenia in some patients

### How Long Until It Works

- Psychotic symptoms can improve with high doses within 1 week, but it may take several weeks for full effect on behavior
- Anxiolytic actions can improve with low doses within 1 week, but it may take several days to weeks for full effect on behavior

### If It Works

- High doses most often reduce positive symptoms in schizophrenia but do not eliminate them
- Low doses most often reduce anxiety symptoms in psychotic and nonpsychotic disorders
- Most schizophrenia 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
- For symptomatic treatment of anxiety in psychotic and nonpsychotic disorders, treatment may also need to be indefinite while monitoring the risks versus the benefits of long-term treatment
- 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, consider switching to a mood stabilizer and/or an atypical antipsychotic for long-term mood stabilization and maintenance

### If It Doesn't Work

- For treatment of psychotic symptoms, consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpiride)
- Consider trying another conventional antipsychotic
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- For treatment of anxiety symptoms, consider adding a benzodiazepine or switching to a benzodiazepine



### Best Augmenting Combos for Partial Response or Treatment Resistance

- Generally, best to switch to another agent
- 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 for short-term agitation
- Addition of antidepressants for severe depression

**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 glucose 100–125 mg/dL), diabetes (fasting plasma glucose >125 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 cyamemazine 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 at antipsychotic (high) doses
- Much lower propensity to cause motor side effects at low doses used to treat anxiety
- By blocking dopamine 2 receptors in the pituitary, it can cause elevations in prolactin, but unlike other conventional antipsychotics, prolactin elevations at low doses of cyamemazine are uncommon or transient
- 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, especially at high doses, may cause sedation, blurred vision, constipation, dry mouth
- Antihistamine actions may contribute to anxiolytic actions at low doses and to sedation and weight gain at high doses
- By blocking alpha 1 adrenergic receptors, cyamemazine can cause dizziness, sedation, and hypotension especially at high doses
- Mechanism of weight gain and any possible increased incidence of diabetes and dyslipidemia with conventional antipsychotics is unknown

**Notable Side Effects**

- \* Neuroleptic-induced deficit syndrome (unusual at low doses)
- Akathisia
- Extrapyrimal symptoms, parkinsonism, tardive dyskinesia (unusual at low doses)
- Galactorrhoea, amenorrhoea (unusual at low doses)
- Hypotension, tachycardia (unusual at low doses)
- Dry mouth, constipation, vision disturbance, urinary retention
- Sedation
- Decreased sweating
- Weight gain (may be unusual at low doses)
- Sexual dysfunction
- Metabolic effects, glucose tolerance



### Life-Threatening or Dangerous Side Effects

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

### Weight Gain



- Reported but not expected especially at low doses

### Sedation



- Many experience and/or can be significant in amount, especially at high doses
- Sedation is usually dose-dependent and may not be experienced as sedation but as anxiolytic actions on anxiety and aggression at low doses where cyamemazine may function as an atypical antipsychotic (e.g., <300 mg/day; especially 25–100 mg/day)

### 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

- Bzotroprine or trihexyphenidyl 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

- 50–300 mg at bedtime for treatment of psychosis
- 25–100 mg for anxiety; duration of treatment 4 weeks
- Children (ages 6 and older): 1–4 mg/kg per day
- Injection: 25–100 mg/day

### Dosage Forms

- Tablet 25 mg, 100 mg
- Oral solution 40 mg/mL
- Injection 50 mg/5 mL

### How to Dose

- Psychosis: usual maintenance dose 50–300 mg at bedtime; maximum dose 600 mg/day divided into 2 or 3 doses; after 2 weeks consider reducing to lowest effective dose
- Anxiety (adults): usual dose 25–100 mg/day; reduce dose if unacceptable sedation; maximum duration of treatment 4 weeks
- Anxiety (children): usual dose 1–4 mg/kg per day



### Dosing Tips

- Has conventional antipsychotic properties at originally recommended high doses (300–600 mg/day)
- ✳ Binding studies, PET studies and clinical observations suggest that cyamemazine may be “atypical” with low motor side effects or prolactin elevations at low doses (below 300 mg/day)
- ✳ Clinical evidence suggests substantial anxiolytic benefits at 25–100 mg/day in many patients
- ✳ Clinical evidence suggests low EPS, little prolactin elevation yet demonstrable anxiolytic, anti-aggression and antidepressant actions at doses below 300 mg/day
- Robust antipsychotic actions on positive symptoms may require dosing above 300 mg/day
- Low doses up to 100 mg/day may be used to augment partial responders to other conventional or atypical antipsychotics, especially for anxiolytic actions
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm<sup>3</sup>

**Overdose**

- Extrapyramidal symptoms, sedation, hypotension, coma, respiratory depression

**Long-Term Use**

- Some side effects may be irreversible (e.g., tardive dyskinesia)

**Habit Forming**

- No

**How to Stop**

- Slow down titration (over 6–8 weeks), especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
- Rapid oral discontinuation of high doses of phenothiazines in psychotic patients may lead to rebound psychosis and worsening of symptoms
- If antiparkinsonian agents are being used, they should generally be continued for a few weeks after high-dose cyamemazine is discontinued

**Pharmacokinetics**

- Half-life 10 hours



**Drug Interactions**

- May decrease the effects of levodopa; contraindicated for use with dopamine agonists other than levodopa
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions phenothiazines may antagonize
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- 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 when administered with a phenothiazine



**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 phenothiazines can lower 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 effects of phenothiazines 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) as for other phenothiazines
- Use only with caution or at low doses, if at all, in Parkinson's disease or Lewy body dementia
- Because cyamemazine may dose-dependently prolong QTc interval, use with caution in patients who have bradycardia or who are taking drugs that can induce bradycardia (e.g., beta blockers, calcium channel blockers, clonidine, digitalis)
- Because cyamemazine may dose-dependently prolong QTc interval, use with caution in patients who have hyperkalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactides)
- Cyamemazine can increase the QTc interval, potentially causing torsades de pointes-type arrhythmia or sudden death

**Do Not Use**

- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- ✳ If QTc interval greater than 450 msec or if taking an agent capable of prolonging the QTc interval

- If patient is taking sultopride
- If patient is in a comatose state or has CNS depression
- If there is the presence of blood dyscrasias, bone marrow depression, or liver disease
- If there is subcortical brain damage
- If patient has sensitivity to or intolerance of gluten (tablets contain gluten)
- If patient has congenital galactosemy, does not adequately absorb glucose/galactose, or has lactase deficit (tablets contain lactose)
- If patient is intolerant of fructose, does not adequately absorb glucose/galactose, or has sugar-isomaltase deficit (oral solution only; oral solution contains saccharose)
- If there is a proven allergy to cyamemazine
- If there is a known sensitivity to any phenothiazine

## SPECIAL POPULATIONS

### Renal Impairment

- Use with caution

### Hepatic Impairment

- Use with caution

### Cardiac Impairment

- Cardiovascular toxicity can occur, especially orthostatic hypotension

### Elderly

- Elderly patients may be more susceptible to adverse effects
- Lower doses should be used and patient should be monitored closely
- Generally, doses above 100 mg/day are not recommended
- 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

- Sometimes used for severe behavioral disturbances in children ages 6 and older
- Oral solution is preferable to the other formulations



### Pregnancy

- 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
- Phenothiazines 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 phenothiazines or anticonvulsant mood stabilizers if treatment is required during pregnancy

### Breast Feeding

- Unknown if cyamemazine is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
- ✳ Recommended either to discontinue drug or bottle feed

## THE ART OF PSYCHOPHARMACOLOGY

### Potential Advantages

- For anxiety in patients with psychotic illnesses
- For anxiety in patients with nonpsychotic illnesses
- For severe depression

### Potential Disadvantages

- Patients with tardive dyskinesia
- Children
- Elderly

### Primary Target Symptoms

- Anxiety associated with psychosis
- Anxiety

- Aggression
- Agitation
- Positive symptoms of psychosis
- Severe depression



**Pearls**

- One of the most frequently prescribed antipsychotics in France, especially as a low-dose anxiolytic for psychotic patients
- \* Appears to have unique anxiolytic actions at low doses without rebound anxiety following discontinuation
- \* Low doses rarely associated with motor side effects or with prolactin elevation

- \* Recently discovered to be a serotonin dopamine antagonist with more potent binding of 5HT2A and 5HT2C receptors than D2 receptors (binding studies and PET scans)
- Low doses appear to saturate 5HT2A receptors in frontal cortex while not saturating D2 receptors in the striatum, accounting for apparent atypical antipsychotic and anxiolytic properties at low doses
- May be useful second-line therapy in facilitating benzodiazepine withdrawal for those patients in whom substitution with another benzodiazepine is not effective or is not appropriate



**Suggested Reading**

Lemoine P, Kermadi I, Garcia-Acosta S, Garay RP, Dib M. Double-blind, comparative study of cyamemazine vs. bromazepam in the benzodiazepine withdrawal syndrome. *Prog Neuropsychopharmacol Biol Psychiatry* 2006;30(1):131–7.

Hameg A, Bayle F, Nuss P, Dupuis P, et al. Affinity of cyamemazine, an anxiolytic antipsychotic drug, for human recombinant

dopamine vs. serotonin receptor subtypes. *Biochem Pharmacol* 2003;65(3):435–40.

Hode Y, Reimold M, Demazieres A, et al. A positron emission tomography (PET) study of cerebral dopamine D2 and serotonin 5-HT2A receptor occupancy in patients treated with cyamemazine (Tercian). *Psychopharmacology (Berl)* 2005;180(2):377–84.