

THERAPEUTICS

Brands • Lodopin
• Zoleptil

see *index* for additional brand names

Generic? No



Class

- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAN)
- Atypical antipsychotic (serotonin-dopamine antagonist)

Commonly Prescribed for

(bold for FDA approved)

- Schizophrenia
- Other psychotic disorders
- Mania



How the Drug Works

- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
- Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognitive and affective symptoms
- Interactions at a myriad of other neurotransmitter receptors may contribute to zotepine's efficacy
- ✳ Specifically inhibits norepinephrine uptake

How Long Until It Works

- Psychotic and manic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition and affective stabilization
- Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients require up to 16–20 weeks to show a good response, especially on cognitive symptoms

If It Works

- Most often reduces positive symptoms in schizophrenia but does not eliminate them
- Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia

- Most schizophrenic patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
- Perhaps 5–15% of schizophrenic patients can experience an overall improvement of greater than 50–60%, especially when receiving stable treatment for more than a year
- Such patients are considered super-responders or “awakeners” since they may be well enough to be employed, live independently, and sustain long-term relationships
- Many bipolar patients may experience a reduction of symptoms by half or more
- Continue treatment until reaching a plateau of improvement
- After reaching a satisfactory plateau, continue treatment for at least a year after first episode of psychosis
- For second and subsequent episodes of psychosis, treatment may need to be indefinite
- Even for first episodes of psychosis, it may be preferable to continue treatment indefinitely to avoid subsequent episodes
- Treatment may not only reduce mania but also prevent recurrences of mania in bipolar disorder

If It Doesn't Work

- Consider trying one of the first-line atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, amisulpride, asenapine, iloperidone, lurasidone)
- If 2 or more antipsychotic monotherapies do not work, consider clozapine
- Some patients may require treatment with a conventional antipsychotic
- If no first-line atypical antipsychotic is effective, consider higher doses or augmentation with valproate or lamotrigine
- Consider noncompliance and switch to another antipsychotic with fewer side effects or to an antipsychotic that can be given by depot injection
- Consider initiating rehabilitation and psychotherapy such as cognitive remediation
- Consider presence of concomitant drug abuse



Best Augmenting Combos for Partial Response or Treatment Resistance

- Augmentation of zotepine has not been systematically studied

- Valproic acid (valproate, divalproex, divalproex ER)
- Other mood-stabilizing anticonvulsants (carbamazepine, oxcarbazepine, lamotrigine)
- Lithium
- Benzodiazepines

Tests

- * Although risk of diabetes and dyslipidemia with zotepine has not been systematically studied, monitoring as for all other atypical antipsychotics is suggested

Before starting an atypical antipsychotic

- * Weigh all patients and track BMI during treatment
- Get baseline personal and family history of diabetes, obesity, dyslipidemia, hypertension, and cardiovascular disease
- * Get waist circumference (at umbilicus), blood pressure, fasting plasma glucose, and fasting lipid profile
- Determine if the patient is
 - overweight (BMI 25.0–29.9)
 - obese (BMI \geq 30)
 - has pre-diabetes (fasting plasma glucose 100–125 mg/dL)
 - has diabetes (fasting plasma glucose $>$ 126 mg/dL)
 - has hypertension (BP $>$ 140/90 mm Hg)
 - has dyslipidemia (increased total cholesterol, LDL cholesterol, and triglycerides; decreased HDL cholesterol)
- Treat or refer such patients for treatment, including nutrition and weight management, physical activity counseling, smoking cessation, and medical management

Monitoring after starting an atypical antipsychotic

- * BMI monthly for 3 months, then quarterly
- * Consider monitoring fasting triglycerides monthly for several months in patients at high risk for metabolic complications and when initiating or switching antipsychotics
- * Blood pressure, fasting plasma glucose, fasting lipids within 3 months and then annually, but earlier and more frequently for patients with diabetes or who have gained $>$ 5% of initial weight
- Treat or refer for treatment and consider switching to another atypical antipsychotic for patients who become overweight, obese, pre-diabetic, diabetic, hypertensive, or dyslipidemic while receiving an atypical antipsychotic

- * Even in patients without known diabetes, be vigilant for the rare but life-threatening onset of diabetic ketoacidosis, which always requires immediate treatment, by monitoring for the rapid onset of polyuria, polydipsia, weight loss, nausea, vomiting, dehydration, rapid respiration, weakness, and clouding of sensorium, even coma
- EKGs may be useful for selected patients (e.g., those with personal or family history of QTc prolongation; cardiac arrhythmia; recent myocardial infarction; uncompensated heart failure; or those taking agents that prolong QTc interval such as pimozide, thioridazine, selected antiarrhythmics, moxifloxacin, sparfloxacin, etc.)
- Patients at risk for electrolyte disturbances (e.g., patients on diuretic therapy) should have baseline and periodic serum potassium and magnesium measurements
- Patients with suspected hematologic abnormalities may require a white blood cell count before initiating treatment
- Monitor liver function tests in patients with established liver disease
- Should check blood pressure in the elderly before starting and for the first few weeks of treatment
- 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 zotepine 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 alpha 1 adrenergic receptors, it can cause dizziness, sedation, and hypotension
- By blocking histamine 1 receptors in the brain, it can cause sedation and weight gain
- 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

- Mechanism of weight gain and possible increased incidence of dyslipidemia and diabetes of atypical antipsychotics is unknown

Notable Side Effects

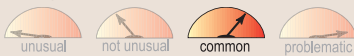
- Atypical antipsychotics may increase the risk for diabetes and dyslipidemia, although the specific risks associated with zotepine are unknown
- Agitation, anxiety, depression, asthenia, headache, insomnia, sedation, hypo/hyperthermia
- Constipation, dry mouth, dyspepsia, weight gain
- Tachycardia, hypotension, sweating, blurred vision
- Rare tardive dyskinesia
- Dose-related hyperprolactinemia



Life-Threatening or Dangerous Side Effects

- Rare neuroleptic malignant syndrome
- Rare seizures (risk increases with dose, especially over 300 mg/day)
- Blood dyscrasias
- Dose-dependent QTc prolongation
- 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



- Many experience and/or can be significant in amount

What to Do About Side Effects

- Wait
- Wait
- Wait
- For motor symptoms, add an anticholinergic agent
- Take more of the dose at bedtime to help reduce daytime sedation
- Weight loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia

- Reduce the dose
- Switch to a first-line atypical antipsychotic

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

- 75–300 mg/day in 3 divided doses

Dosage Forms

- Tablet 25 mg, 50 mg, 100 mg

How to Dose

- Initial 75 mg/day in 3 doses; can increase every 4 days; maximum 300 mg/day in 3 doses



Dosing Tips

- Slow initial titration can minimize hypotension
- No formal studies, but some patients may do well on twice daily dosing rather than 3 times daily dosing
- ✳ Dose-related QTc prolongation, so use with caution, especially at high doses
- Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³

Overdose

- Can be fatal, especially in mixed overdoses; seizures, coma

Long-Term Use

- Can be used to delay relapse in long-term treatment of schizophrenia

Habit Forming

- No

How to Stop

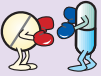
- Slow down-titration (over 6 to 8 weeks), especially when simultaneously beginning

a new antipsychotic while switching (i.e., cross-titration)

- Rapid 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 zotepine is discontinued

Pharmacokinetics

- Metabolized by CYP450 3A4 and CYP450 1A2
- Active metabolite norzotepine



Drug Interactions

- Combined use with phenothiazines may increase risk of seizures
- Can decrease the effects of levodopa, dopamine agonists
- Epinephrine may lower blood pressure
- May interact with hypotensive agents due to alpha 1 adrenergic blockade
- May enhance QTc prolongation of other drugs capable of prolonging QTc interval
- Plasma concentrations increased by diazepam, fluoxetine
- Zotepine may increase plasma levels of phenytoin
- May increase risk of bleeding if used with anticoagulants
- Theoretically, dose may need to be raised if given in conjunction with CYP450 1A2 inducers (e.g., cigarette smoke)
- Theoretically, dose may need to be lowered if given in conjunction with CYP450 1A2 inhibitors (e.g., fluvoxamine) in order to prevent dangers of dose-dependent QTc prolongation
- Theoretically, dose may need to be lowered if given in conjunction with CYP450 3A4 inhibitors (e.g., fluvoxamine, nefazodone, fluoxetine) in order to prevent dangers of dose-dependent QTc prolongation



Other Warnings/ Precautions

- Not recommended for use with sibutramine
- Use cautiously in patients with alcohol withdrawal or convulsive disorders because of possible lowering of seizure threshold
- If signs of neuroleptic malignant syndrome develop, treatment should be immediately discontinued

- Because zotepine 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 zotepine may dose-dependently prolong QTc interval, use with caution in patients who have hypokalemia and/or hypomagnesemia or who are taking drugs that can induce hypokalemia and/or magnesemia (e.g., diuretics, stimulant laxatives, intravenous amphotericin B, glucocorticoids, tetracosactide)
- Because zotepine dose-dependently prolongs QTc interval, use with caution in patients taking any agent capable of increasing zotepine plasma levels (e.g., diazepam, CYP450 1A2 inhibitors, and CYP450 3A4 inhibitors)

Do Not Use

- If patient has epilepsy or family history of epilepsy
- If patient has gout or history of nephrolithiasis
- If patient is taking other CNS depressants
- If patient is taking high doses of other antipsychotics
- If patient is taking agents capable of significantly prolonging QTc interval (e.g., pimozide; thioridazine; selected antiarrhythmics such as quinidine, disopyramide, amiodarone, and sotalol; selected antibiotics such as moxifloxacin and sparfloxacin)
- If there is a history of QTc prolongation or cardiac arrhythmia, recent acute myocardial infarction, uncompensated heart failure
- If patient is pregnant or breast feeding
- If there is a proven allergy to zotepine

SPECIAL POPULATIONS

Renal Impairment

- Recommended starting dose 25 mg twice a day; recommended maximum dose generally 75 mg twice a day

Hepatic Impairment

- Recommended starting dose 25 mg twice a day; recommended maximum dose generally 75 mg twice a day

- May require weekly monitoring of liver function during the first few months of treatment

Cardiac Impairment

- Drug should be used with caution
- Zotepine produces a dose-dependent prolongation of QTc interval, which may be enhanced by the existence of bradycardia, hypokalemia, congenital or acquired long QTc interval, which should be evaluated prior to administering zotepine
- Use with caution if treating concomitantly with a medication likely to produce prolonged bradycardia, hypokalemia, slowing of intracardiac conduction, or prolongation of the QTc interval
- Avoid zotepine in patients with a known history of QTc prolongation, recent acute myocardial infarction, and uncompensated heart failure

Elderly

- Recommended starting dose 25 mg twice a day; recommended maximum dose generally 75 mg twice a day
- Although atypical 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 atypical antipsychotics are at an 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 under age 18



Pregnancy

- Insufficient data in humans to determine risk
- 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

- Zotepine is not recommended during pregnancy

Breast Feeding

- Zotepine is not recommended during breast feeding
- Immediate postpartum period is a high-risk time for relapse of psychosis, so may consider treatment with another antipsychotic

THE ART OF PSYCHOPHARMACOLOGY

Potential Advantages

- Norepinephrine reuptake blocking actions have theoretical benefits for cognition (attention) and for depression

Potential Disadvantages

- Patients not compliant with 3 times daily dosing
- Patients requiring rapid onset of antipsychotic action
- Patients with uncontrolled seizures

Primary Target Symptoms

- Positive symptoms of psychosis
- Negative symptoms of psychosis
- Cognitive functioning
- Depressive symptoms



Pearls

- ✳️ Zotepine inhibits norepinephrine reuptake, which may have implications for treatment of depression, as well as for cognitive symptoms of schizophrenia
- Risks of diabetes and dyslipidemia not well studied for zotepine, but known significant weight gain suggests the need for careful monitoring during zotepine treatment
- Not as well investigated in bipolar disorder, but its mechanism of action suggests efficacy in acute bipolar mania



Suggested Reading

Ackenheil M. [The biochemical effect profile of zotepine in comparison with other neuroleptics]. *Fortschr Neurol Psychiatr* 1991;59(Suppl 1):S2–9.

Fenton M, Morris S, De-Silva P, et al. Zotepine for schizophrenia. *Cochrane Database Syst Rev* 2000;(2):CD001948.

Stanniland C, Taylor D. Tolerability of atypical antipsychotics. *Drug Saf* 2000;22(3):195–214.