**THERAPEUTICS**

**Brands**
- Loxitane
- Adasuve (Staccato loxapine, inhaled loxapine)

*see index for additional brand names*

**Generic?** Yes

**Class**
- Neuroscience-based Nomenclature: dopamine and serotonin receptor antagonist (DS-RAn)
- Conventional antipsychotic (neuroleptic, dopamine 2 antagonist, serotonin dopamine antagonist)

**Commonly Prescribed for**
(bold for FDA approved)
- Schizophrenia
- Acute treatment of agitation associated with schizophrenia or bipolar disorder
- Other psychotic disorders
- Bipolar disorder

**How the Drug Works**
- Blocks dopamine 2 receptors, reducing positive symptoms of psychosis
  - Although classified as a conventional antipsychotic, loxapine is a potent serotonin 2A antagonist
  - Serotonin 2A antagonist properties might be relevant at low doses, but generally are overwhelmed by high dosing

**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, asenapine, iloperidone, lurasidone, 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
LOXAPINE (continued)

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 loxapine should be discontinued at the first sign of decline of WBC in the absence of other causative factors.

Galactorrhea, amenorrhea
- Sedation
- Dry mouth, constipation, vision disturbance, urinary retention
- Hypotension, tachycardia

Life-Threatening or Dangerous Side Effects
- Rare neuroleptic malignant syndrome
- Rare agranulocytosis
- Rare hepatocellular injury
- Rare seizures
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis
- Bronchosperm, with the potential to lead to respiratory distress and respiratory arrest (inhalant)

Weight Gain
- Reported but not expected

Sedation
- Many experience and/or can be significant in amount
- Sedation is usually transient
- Sedation is usually dose-dependent and may not be experienced at low doses where loxapine may function as an atypical antipsychotic (e.g., <50 mg/day; especially 5–25 mg/day)

What to Do About Side Effects
- 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

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
- Extrapyramidal symptoms, parkinsonism, tardive dyskinesia
To augment partial responders to an atypical antipsychotic, consider doses of loxapine as low as 5–60 mg/day, but use full doses if necessary. No formal studies, but some patients may do well on once daily dosing, especially at night, rather than twice daily dosing. Available as 5-mg and 10-mg capsules for low-dose use and as 25-mg and 50-mg capsules for routine use. Available as a liquid dosage formulation. Available for acute inhalation administration. Prior to administering inhalation powder, screen all patients for a history of pulmonary disease, and examine patients (including chest auscultation) for respiratory abnormalities (e.g., wheezing). After administering inhalation powder, monitor patients for signs and symptoms of bronchospasm at least every 15 minutes for at least an hour. Available for acute intramuscular administration (50 mg/mL). Intramuscular loxapine may have faster onset of action and superior efficacy for agitated/excited and aggressive behavior in some patients than intramuscular haloperidol. In the acute situation, give 25–50 mg intramuscularly (0.5–1.0 mL of 50 mg/mL solution) with onset of action within 60 minutes. When initiating therapy with an atypical antipsychotic in an acute situation, consider short-term intramuscular loxapine to “lead in” to orally administered atypical; e.g., initiate oral dosing of an atypical antipsychotic with 25–50 mg loxapine 2–3 times a day intramuscularly to achieve antipsychotic effects without extrapyramidal symptoms and sedation. When using loxapine to “top-up” previously stabilized patients now decompensating, may use loxapine as single 25–50 mg doses as needed intramuscularly or as oral liquid or tablets. Patients receiving atypical antipsychotics may occasionally require a “top up” of a conventional antipsychotic to control aggression or violent behavior. Treatment should be suspended if absolute neutrophil count falls below 1,000/mm³.

**DOSING AND USE**

**Usual Dosage Range**
- 60–100 mg/day in divided doses

**Dosage Forms**
- Capsule 6.8 mg loxapine succinate equivalent to 5 mg loxapine, 13.6 mg loxapine succinate equivalent to 10 mg loxapine, 34.0 mg loxapine succinate equivalent to 25 mg loxapine, 68.1 mg loxapine succinate equivalent to 50 mg loxapine
- Oral liquid 25 mg/mL
- Injection 50 mg/mL
- Inhalant 10 mg unit in a single-use inhaler

**How to Dose**
- Initial 20 mg/day in 2 doses; titrate over 7–10 days to 60–100 mg/day in 2–4 doses; maximum generally 250 mg/day
- Take liquid formulation in orange or grapefruit juice
- Inhalation powder: 10 mg by oral inhalation using an inhaler; only 1 dose per 24 hours; must be administered by a health-care professional in a setting with immediate onsite access to equipment and personnel trained to manage acute bronchospasm, including advanced airway management

**Dosing Tips**
- Has conventional antipsychotic properties at originally recommended doses (i.e., starting at 10 mg twice a day, maintenance 60–100 mg/day, maximum 250 mg/day given in 2 divided doses)
- Binding studies, PET studies, and anecdotal clinical observations suggest that loxapine may be atypical at lower doses (perhaps 5–30 mg/day) but further studies needed
- Anecdotal evidence that many patients can be maintained at 20–60 mg/day as monotherapy
LOXAPINE (continued)

Overdose
- Deaths have occurred; extrapyramidal symptoms, CNS depression, cardiovascular effects, hypotension, seizures, respiratory depression, renal failure, coma

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

Habit Forming
- No

How to Stop
- Slow down-titration of oral formulation (at least 4 weeks when possible), 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 loxapine is discontinued

Pharmacokinetics
- Half-life approximately 4 hours for oral formulation
- Half-life approximately 12 hours for intramuscular formulation
- Multiple active metabolites with longer half-lives than parent drug
- \( \text{N} \)-desmethyl loxapine is amoxapine, an antidepressant
- 8-hydroxyloxapine and 7-hydroxyloxapine are also serotonin-dopamine antagonists
- 8-hydroxyamoxapine and 7-hydroxyamoxapine are also serotonin-dopamine antagonists

Drug Interactions
- Respiratory depression may occur when loxapine is combined with lorazepam
- Additive effects may occur if used with CNS depressants
- May decrease the effects of levodopa, dopamine agonists
- 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
- May increase the effects of antihypertensive drugs except for guanethidine, whose antihypertensive actions loxapine may antagonize

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
- 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 cautiously in patients with glaucoma, urinary retention
- Observe for signs of ocular toxicity (pigmentary retinopathy, lenticular pigmentation)
- Avoid extreme heat exposure
- Use only with caution if at all in Parkinson’s disease or Lewy body dementia

Do Not Use
- If patient is in a comatose state or has CNS depression
- If patient has asthma or history of asthma, COPD, other lung disease associated with bronchospasm, acute respiratory signs/symptoms, current use of medications to treat airways, history of bronchospasm following treatment with loxapine inhalation powder (inhalant only)
- If there is a proven allergy to loxapine
- If there is a known sensitivity to any dibenzoxazepine

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
- 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
- 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 (PLLRL or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
- Controlled studies have not been conducted in pregnant women
- 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
- Renal papillary abnormalities have been seen in rats 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**

- Unknown if loxapine 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

- Intramuscular formulation for emergency use

### Potential Disadvantages

- Patients with tardive dyskinesia

### Primary Target Symptoms

- Positive symptoms of psychosis
- Motor and autonomic hyperactivity
- Violent or aggressive behavior

### Pearls

- Recently discovered to be a serotonin dopamine antagonist (binding studies and PET scans)
- Active metabolites are also serotonin dopamine antagonists with longer half-lives than parent drug, thus possibly allowing once daily treatment
- One active metabolite is an antidepressant (amoxapine, also known as N-desmethyl-loxapine)
- Theoretically, loxapine should have antidepressant actions, especially at high doses, but no controlled studies
- Theoretically, loxapine may have advantages for short-term use in some patients with psychotic depression
- Developed as a conventional antipsychotic; i.e., reduces positive symptoms, but causes extrapyramidal symptoms and prolactin elevations
- Lower extrapyramidal symptoms than haloperidol in some studies, but not fixed-dose studies and no low-dose studies
- Causes less weight gain than other antipsychotics, both atypical and conventional, and may even be associated with weight loss
- No formal studies of negative symptoms, but some studies show superiority to...
Suggested Reading


