THERAPEUTICS

Brands • LATUDA
see index for additional brand names

Generic? No

Class
• Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotic; also a potential mood stabilizer)

Commonly Prescribed for
(bold for FDA approved)
• Schizophrenia
• Acute mania/mixed mania
• Other psychotic disorders
• Bipolar maintenance
• Bipolar depression
• Treatment-resistant depression
• Behavioral disturbances in dementia
• Behavioral disturbances in children and adolescents
• Disorders associated with problems with impulse control

How the Drug Works
• Blocks dopamine 2 receptors, reducing positive symptoms of psychosis and stabilizing affective symptoms
• Blocks serotonin 2A receptors, causing enhancement of dopamine release in certain brain regions and thus reducing motor side effects and possibly improving cognition and affective symptoms
• Potently blocks serotonin 7 receptors, which may be beneficial for mood, sleep, cognitive impairment and negative symptoms in schizophrenia, and also in bipolar disorder and major depressive disorder
• Partial agonist at 5HT1A receptors, and antagonist actions at alpha 2A and alpha 2C receptors, which may be beneficial for mood, anxiety and cognition in a number of disorders
• Lacks potent actions at dopamine D1, muscarinic M1 and histamine H1 receptors, theoretically suggesting less propensity for inducing cognitive impairment, weight gain or sedation compared to other agents with these properties

How Long Until It Works
• Psychotic symptoms can improve within 1 week, but it may take several weeks for full effect on behavior as well as on cognition
• Classically recommended to wait at least 4–6 weeks to determine efficacy of drug, but in practice some patients may require up to 16–20 weeks to show a good response, especially on cognitive impairment and functional outcome

If It Works
• Most often reduces positive symptoms but does not eliminate them
• Can improve negative symptoms, as well as aggressive, cognitive, and affective symptoms in schizophrenia
• Most schizophrenia patients do not have a total remission of symptoms but rather a reduction of symptoms by about a third
• Perhaps 5–15% of schizophrenia 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
• 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

If It Doesn’t Work
• Try one of the other atypical antipsychotics (risperidone, olanzapine, quetiapine, ziprasidone, aripiprazole, paliperidone, asenapine, iloperidone, amisulpride)
• 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.
- Consider presence of concomitant drug abuse.

Best Augmenting Combos for Partial Response or Treatment Resistance
- Valproic acid (valproate, divalproex, divalproex ER)
- Mood stabilizing anticonvulsants (see drug interactions)
- Lithium
- Benzodiazepines

Tests
Before starting any 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 ≥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 any 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.
- 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 lurasidone should be discontinued at the first sign of decline in WBC in the absence of other causative factors (class warning).

SIDE EFFECTS
How Drug Causes Side Effects (Class 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.
- Mechanism of weight gain and increased incidence of diabetes and dyslipidemia with atypical antipsychotics is unknown.

Notable Side Effects
- Sedation (somnolence).
- Akathisia.
- Nausea.
- Any atypical antipsychotic may increase risk for diabetes and dyslipidemia (class warning).
- Any atypical antipsychotic may cause tardive dyskinesia (much reduced risk compared to conventional antipsychotics) (class warning).
Life-Threatening or Dangerous Side Effects

- Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients taking atypical antipsychotics (class warning)
- Increased risk of death and cerebrovascular events in elderly patients with dementia-related psychosis (class warning)
- Rare neuroleptic malignant syndrome (much reduced risk compared to conventional antipsychotics) (class warning)
- Rare seizures (class warning)

Weight Gain

Short Term

- Many experience about one to two pound weight gain greater than placebo in short term 6 week trials

Long Term

- Patients in long term 52 week trials actually lost 1.5 pounds on average
- Clinical experience, however, is still limited
- Appears to be less weight gain than observed with some antipsychotics
- Many patients lost weight in long term trials when switching from olanzapine to lurasidone

Sedation

- May be higher in short term trials than in long term use

What to Do About Side Effects

- Wait
- Wait
- Wait
- Anticholinergics may reduce motor side effects when present
- Dose reduction may reduce akathisia when present
- Consider changing to nighttime dosing (with evening meal)

Dosage and Use

Usual Dosage Range

- 40–80 mg/day
- Some patients may benefit from doses up to 160 mg/day

Dosage Forms

- Tablet 40 mg, 80 mg

How to Dose

- Initial 40–80 mg once daily
- Dose titration to initial dose of 40 mg/day is not required
- Consider dose increases from 40 mg/day up to 160 mg/day as necessary and as tolerated

Dosing Tips

- Lurasidone should be taken with food (i.e., at least a small meal of a minimum of 350 calories)
- Lurasidone absorption can be decreased by up to 50% on an empty stomach and more consistent efficacy will be seen if dosing is done regularly with food
- Once daily dosing
- 40–80 mg per day was suggested by controlled clinical trials as adequate for many patients
- Some patients benefit from higher dosing, with controlled clinical trials up to 160 mg/day
- Higher doses may benefit more difficult patients with treatment nonresponsiveness to other agents
- Higher dosing, however, may cause more side effects
• Taking lurasidone at night may reduce side effects, especially sedation and motor side effects

**Overdose**
• Limited data

**Long-Term Use**
• Not extensively studied past 52 weeks, but long-term maintenance treatment is often necessary for schizophrenia
• Should periodically reevaluate long term usefulness in individual patients, but treatment may need to continue for many years in patients with schizophrenia

**Habit Forming**
• No

**How to Stop**
• Down-titration, especially when simultaneously beginning a new antipsychotic while switching (i.e., cross-titration)
• Rapid discontinuation could theoretically lead to rebound psychosis and worsening of symptoms

**Pharmacokinetics**
• Half-life 18–31 hours (shorter half life better documented at the 40 mg dose)
• Metabolized by CYP450 3A4

**Drug Interactions**
• Inhibitors of CYP450 3A4 (e.g., nefazodone, fluvoxamine, fluoxetine, ketoconazole) may increase plasma levels of lurasidone
• Coadministration of lurasidone with a strong CYP450 3A4 inhibitor (e.g., ketoconazole) or with a strong CYP450 3A4 inducer (e.g., rifampin) is contraindicated
• Coadministration of lurasidone with moderate CYP450 3A4 inhibitors can be considered
• Moderate inducers of CYP450 3A4 may decrease plasma levels of lurasidone
• May increase effects of antihypertensive agents
• May antagonize levodopa, dopamine agonists

**Other Warnings/Precautions**
• Use with caution in patients with conditions that predispose to hypotension (dehydration, overheating)
• Dysphagia has been associated with antipsychotic use, and lurasidone should be used cautiously in patients at risk for aspiration pneumonia

**Do Not Use**
• If there is a proven allergy to lurasidone
• In patients with a history of angioedema
• In patients taking ketoconazole or rifampin

**SPECIAL POPULATIONS**

**Renal Impairment**
• Maximum dose should not exceed 40 mg for patients with moderate or severe renal impairment

**Hepatic Impairment**
• Maximum dose should not exceed 40 mg for patients with moderate or severe hepatic impairment

**Cardiac Impairment**
• Should be used with caution because of theoretical risk of orthostatic hypotension, although low potency at alpha 1 receptors suggest this risk may be less than for some other antipsychotics
• Lurasidone does not have a warning for QTc prolongation

**Elderly**
• In general, no dose adjustment is necessary for elderly patients
• However, some elderly patients may tolerate lower doses better
• 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
LURASIDONE

Although human studies are inadequate, animal finds are negative
• Other antipsychotics are higher risk categories for pregnancy

Potential Disadvantages
• Patients who cannot take a medication consistently with food

Primary Target Symptoms
• Positive symptoms of psychosis
• Negative symptoms of psychosis
• Cognitive symptoms
• Unstable mood (both depression and mania)
• Aggressive symptoms

Potential Advantages
• Patients requiring rapid onset of antipsychotic action without dosage titration
• Patients who wish to take an antipsychotic once a day
• Patients experiencing weight gain from other antipsychotics or who wish to avoid weight gain
• Possibly in pregnant women or women of child bearing potential as lurasidone is the only antipsychotic with a category B rating (i.e., no evidence of risk in humans and animal finds are negative)

Children and Adolescents
• Safety and efficacy have not been established
• Children and adolescents using lurasidone may need to be monitored more often than adults

Pregnancy
• Risk Category B [no evidence of risk in humans; no adequate human studies have been performed but animal studies are negative]
• Not teratogenic in rodents
• Psychotic symptoms may worsen during pregnancy and some form of treatment may be necessary
• Lurasidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy
• Pregnancy exposure should be reported to the manufacturer and a national pregnancy registry, where available

Breast Feeding
• Unknown if lurasidone is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
• Recommended either to discontinue drug or bottle feed unless the potential benefit to the mother justifies the potential risk to the child
• Infants of women who choose to breast feed while on lurasidone should be monitored for possible adverse effects

Pearls
• Clinical trials suggest that lurasidone is well-tolerated with a favorable balance of efficacy and safety
• One of the few “metabolically friendly” antipsychotics
  • Neutral for weight gain (1–2 pounds weight gain in short term studies, with 1–2 pounds weight loss in long term studies)
  • Neutral for lipids (triglycerides and cholesterol)
  • Neutral for glucose
• Only atypical antipsychotic documented not to cause QTc prolongation, and one of the few atypical antipsychotics without a QTc warning
• Only first-line atypical antipsychotic with lower risk category B warning for pregnancy
• Seems to have low-level extrapyramidal side effects, but real-world clinical experience is required to confirm this
• Somnolence and akathisia are the most common side effects in short term clinical trials that dosed lurasidone in the daytime, but these adverse effects were reduced in a controlled study of lurasidone administered at night with food
• Prolactin elevations low and generally transient
• Nausea and agitation experienced by some patients
• Widespread clinical use will be necessary to confirm these tolerability findings suggested from controlled clinical trials

THE ART OF PSYCHOPHARMACOLOGY

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LURASIDONE (continued)

- Receptor binding profile suggests favorable potential as an antidepressant
  - 5HT7 antagonism is antidepressant in animal models and has pro-cognitive actions in animal models
  - 5HT7 antagonism and 5HT1A partial agonism enhance serotonin levels in animals treated with SSRIs/SNRIs, suggesting use for lurasidone as an augmenting agent to SSRIs/SNRIs in depression
  - 5HT7 antagonism plus the absence of D1, H1 and M1 antagonism suggest potential for cognitive improvement
- Not approved for mania, but almost all atypical antipsychotics approved for acute treatment of schizophrenia have proven effective in the acute treatment of mania as well

Suggested Reading


