**Therapeutics**

**Brands** • LATUDA

*see index for additional brand names*

**Generic?** No

**Class**
- Neuroscience-based Nomenclature: dopamine, serotonin receptor antagonist (DS-RAn)
- Atypical antipsychotic (serotonin-dopamine antagonist; second generation antipsychotic; also a potential mood stabilizer)

**Commonly Prescribed for**

*(bold for FDA approved)*
- Schizophrenia (ages 13 and older)
- Bipolar depression
  - Acute mania/mixed mania
  - Other psychotic disorders
  - Bipolar maintenance
  - 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 serotonin 7 and 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
LURASIDONE (continued)

- 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
- Dose-dependent sedation
- Akathisia
- Nausea
- Dose-dependent hyperprolactinemia
- May increase risk for diabetes and dyslipidemia
- Rare tardive dyskinesia (much reduced risk compared to conventional antipsychotics)
Weight Loss, exercise programs, and medical management for high BMIs, diabetes, dyslipidemia
Switch to another atypical antipsychotic

Best Augmenting Agents for Side Effects
- Benztropine or trihexyphenidyl for motor side effects
- Beta blockers or benzodiazepines may reduce akathisia when present
- Many side effects cannot be improved with an augmenting agent

Life-Threatening or Dangerous Side Effects
- Tachycardia, first-degree AV block
- 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

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)

DOSING AND USE
Usual Dosage Range
- 40–80 mg/day for schizophrenia
- Some patients with schizophrenia may benefit from doses up to 160 mg/day
- 20–60 mg/day for bipolar depression
- Some patients with bipolar depression may benefit from doses up to 120 mg/day

Dosage Forms
- Tablet 20 mg, 40 mg, 60 mg, 80 mg, 120 mg

How to Dose
- Initial 40–80 mg once daily with food for schizophrenia
- Dose titration to initial dose of 40 mg/day is not required for schizophrenia
- Consider dose increases from 40 mg/day up to 160 mg/day as necessary and as tolerated for schizophrenia
- Initial 20 mg once daily with food for bipolar depression
- Can titrate to 120 mg/day in bipolar depression if necessary and 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
- Giving lurasidone at bedtime can greatly reduce daytime sedation, akathisia, and EPS
LURASIDONE (continued)

- Starting dose for schizophrenia is 40 mg/day, which may be an adequate dose for some patients, especially first-episode and early-onset psychosis cases
- 40–80 mg per day was suggested by controlled clinical trials as adequate for many patients with schizophrenia
- Some patients with schizophrenia benefit from higher dosing, with controlled clinical trials up to 160 mg/day
- Higher doses than 160 mg/day may benefit more difficult patients with schizophrenia with treatment nonresponsiveness to other agents
- Higher dosing, however, may cause more side effects
- Dosing for bipolar depression or major depressive episodes with mixed features is generally lower than for schizophrenia, with a 20 mg starting dose; 20 mg/day may be an adequate dose for some patients
- Doses between 20 and 60 mg/day are generally as efficacious as doses between 60 and 120 mg/day for bipolar depression or major depressive episodes with mixed features
- Some patients with bipolar depression or major depressive episodes with mixed features may require higher doses

Pharmacokinetics
- Half-life 18–31 hours (shorter half-life better documented at the 40 mg dose)
- Metabolized by CYP450 3A4
- Cmax and bioavailability are reduced if taken without food

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; recommended starting dose is 20 mg/day; recommended maximum dose is 80 mg/day
- Moderate inducers of CYP450 3A4 may decrease plasma levels of lurasidone
- May increase effects of antihypertensive agents
- May antagonize levodopa, dopamine agonists

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

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 patient is taking a strong CYP 3A4 inhibitor (e.g., ketoconazole) or inducer (e.g., rifampin)
- In patients with a history of angioedema
- If there is a proven allergy to lurasidone

SPECIAL POPULATIONS

Renal Impairment
- Moderate and severe impairment: initial 20 mg/day; maximum dose 80 mg/day
**Hepatic Impairment**
- Moderate impairment: initial 20 mg/day; maximum dose 80 mg/day
- Severe impairment: initial 20 mg/day; maximum dose 40 mg/day

**Cardiac Impairment**
- Should be used with caution because of theoretical risk of orthostatic hypotension, although low potency at alpha 1 receptors suggests this risk may be less 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

**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**
- 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 (PLLR 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
- Animal studies do not show adverse effects
- 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
- Lurasidone may be preferable to anticonvulsant mood stabilizers if treatment is required during pregnancy

**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

**THE ART OF PSYCHOPHARMACOLOGY**

**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

**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
LURASIDONE (continued)

**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
- Seems to have low-level EPS, especially when dosed at bedtime
- Somnolence and akathisia are the most common side effects in short-term clinical trials of schizophrenia that dosed lurasidone in the daytime, but these adverse effects were reduced in a controlled study of lurasidone administered at night with food
- Nausea and occasional vomiting occurred in bipolar depression studies especially at higher doses
- Nausea and vomiting generally rapidly abates within a few days or can be avoided by slow dose titration and giving lower doses
- Prolactin elevations low and generally transient
- Agitation experienced by some patients
- 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
  - Lack of D1 antagonist, anticholinergic, and antihistamine properties may explain relative lack of cognitive side effects in most patients
- One of the best studied agents for depression with mixed features, showing efficacy in a large randomized controlled trial
- 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
- Patients with inadequate responses to atypical antipsychotics may benefit from determination of plasma drug levels and, if low, a dosage increase even beyond the usual prescribing limits
- Patients with inadequate responses to atypical antipsychotics may also benefit from a trial of augmentation with a conventional antipsychotic or switching to a conventional antipsychotic
- However, long-term polypharmacy with a combination of a conventional antipsychotic 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
**Suggested Reading**


