MONOTHERAPY STUDY

Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study


ADJUNCTIVE THERAPY STUDY

Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study


INDICATIONS AND USAGE

LATUDA is indicated for treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate. The efficacy of LATUDA was established in a 6-week monotherapy study and a 6-week adjunctive therapy study with lithium or valproate in adult patients with bipolar depression. The effectiveness of LATUDA for long-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient. The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

IMPORTANT SAFETY INFORMATION FOR LATUDA

Antidepressants increased the risk of suicidal thoughts and behavior in children, adolescents, and young adults in short-term studies. These studies did not show an increase in the risk of suicidal thoughts and behavior with antidepressant use in patients over age 24; there was a reduction in risk with antidepressant use in patients aged 65 and older. In patients of all ages who are started on antidepressant therapy, monitor closely for worsening, and for emergence of suicidal thoughts and behaviors. Advise families and caregivers of the need for close observation and communication with the prescriber. LATUDA is not approved for use in patients under the age of 18 years.

Please see additional Important Safety Information, including **Boxed Warning**, on back cover, and enclosed full Prescribing Information.
Lurasidone Monotherapy in the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study


Objective

- Evaluate the efficacy and safety of LATUDA as monotherapy in the treatment of patients with major depressive episodes associated with bipolar I disorder

Study design

- Patients were randomized to receive double-blind treatment with LATUDA 20–60 mg/day (n=166), 80–120 mg/day (n=169), or placebo (n=170) for 6 weeks

Endpoints

- **Primary:** Mean change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) scores
- **Key secondary:** Mean change from baseline to Week 6 in Clinical Global Impression scale for use in bipolar illness (CGI-BP) depression scores

Summary of results

- LATUDA 20–60 mg/day and 80–120 mg/day groups had significantly reduced mean MADRS total scores at Week 6 compared with the placebo group
- LATUDA resulted in significantly greater reduction in CGI-BP depression scores at Week 6 compared with placebo
- Discontinuation rates due to adverse events were similar in LATUDA 20–60 mg/day (6.6%) and 80–120 mg/day (5.9%) groups and comparable to placebo group (6.5%)
- Minimal changes in weight, lipids, and glucose were observed during treatment with LATUDA

“Monotherapy with [LATUDA] … significantly reduced depressive symptoms in patients with bipolar I depression. [LATUDA] was well tolerated, with few changes in weight or metabolic parameters.”

IMPORTANT SAFETY INFORMATION FOR LATUDA

LATUDA is contraindicated in the following:
- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)
Lurasidone as Adjunctive Therapy With Lithium or Valproate for the Treatment of Bipolar I Depression: A Randomized, Double-Blind, Placebo-Controlled Study


Objective

Evaluate the efficacy of LATUDA as adjunctive therapy with lithium or valproate for the treatment of bipolar I depression

Study design

Patients who had not adequately responded to ≥28 days of lithium or valproate were randomized to receive 6 weeks of double-blind adjunctive treatment with LATUDA (n=183) or placebo (n=165) added to therapeutic levels of either lithium or valproate. At screening, serum levels for lithium and valproate were required to be 0.6–1.2 mEq/L and 50–125 μg/mL, respectively.

Endpoints

Primary: Mean change from baseline to Week 6 in Montgomery-Åsberg Depression Rating Scale (MADRS) scores

Key secondary: Mean change from baseline to Week 6 in Clinical Global Impression scale for use in bipolar illness (CGI-BP) depression scores

Summary of results

LATUDA 20–120 mg/day as adjunctive therapy with lithium or valproate significantly reduced mean MADRS total scores at Week 6 compared with placebo.

LATUDA resulted in significantly greater reduction in CGI-BP depression scores at Week 6 compared with placebo.

In the LATUDA and placebo groups, discontinuation rates due to adverse events were 6.0% and 7.9%, respectively.

Minimal changes in weight, lipids, and glucose were observed during treatment with LATUDA.

“In patients with bipolar I depression, treatment with [LATUDA] adjunctive to lithium or valproate significantly improved depressive symptoms and was generally well tolerated.”

IMPORTANT SAFETY INFORMATION FOR LATUDA

In placebo-controlled trials with risperidone, aripiprazole, and olanzapine in elderly subjects with dementia, there was a higher incidence of cerebrovascular adverse reactions (cerebrovascular accidents and transient ischemic attacks) including fatalities compared to placebo-treated subjects. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

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ANTIDEPRESSANT EFFICACY RESULTS

- Primary efficacy was measured using the Montgomery-Åsberg Depression Rating Scale (MADRS)\(^1\,^2\)
  - MADRS is a validated scale used to assess severity of depressive symptoms measuring 10 symptoms of depression and giving a total score range from 0 (no depressive symptoms) to 60 (maximum score)\(^3\)

- Key secondary efficacy was measured using the Clinical Global Impression scale for use in bipolar illness (CGI-BP) scale\(^1\,^2\)
  - CGI-BP captures the clinician's global impression of improvement in overall illness severity using a 7-point scale, where a higher score is associated with greater illness severity. This allows for a comparison to the patient's baseline condition and takes into account the impact of side effects on patient functioning\(^3\,^4\)

LATUDA monotherapy significantly reduced depressive symptoms at Week 6 vs placebo

**Table:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline MADRS Score</th>
<th>Week 6 MADRS Score</th>
<th>LS Mean Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATUDA 20–60 mg/day</td>
<td>30.3</td>
<td>14.8</td>
<td>−10.7</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>LATUDA 80–120 mg/day</td>
<td>30.6</td>
<td>15.4</td>
<td>−16.2</td>
<td>(&lt;0.001)</td>
</tr>
<tr>
<td>Placebo</td>
<td>30.5</td>
<td>10.8</td>
<td>−14.7</td>
<td>(&lt;0.001)</td>
</tr>
</tbody>
</table>

- Mean baseline MADRS scores: placebo, 30.5; LATUDA 20–60 mg/day, 30.3; and LATUDA 80–120 mg/day, 30.6\(^6\)
  - The least-squares (LS) mean change from baseline to Week 6 in MADRS total score was −10.7 with placebo, −15.4 with LATUDA 20–60 mg/day (\(<0.001\)), and −15.4 with LATUDA 80–120 mg/day (\(<0.001\)). This translates into a 44% greater reduction in depressive symptoms for LATUDA compared to placebo at Week 6.

- The high-dose range (80–120 mg/day) did not provide additional efficacy, on average, compared to the low-dose range (20–60 mg/day)\(^1\)

- LATUDA was also superior to placebo in the key secondary measure of CGI-BP scores\(^1\)

In patients with inadequate response to lithium or valproate, adding LATUDA significantly reduced depressive symptoms at Week 6 vs placebo

**Table:**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Baseline MADRS Score</th>
<th>Week 6 MADRS Score</th>
<th>LS Mean Change</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium/valproate + LATUDA</td>
<td>30.6</td>
<td>14.9</td>
<td>−13.5</td>
<td>(&lt;0.01)</td>
</tr>
<tr>
<td>Lithium/valproate + Placebo</td>
<td>30.8</td>
<td>17.1</td>
<td>−13.7</td>
<td>(&lt;0.01)</td>
</tr>
</tbody>
</table>

- Mean baseline MADRS scores: placebo, 30.8; LATUDA 20–120 mg/day, 30.6\(^2\)
  - The LS mean change from baseline to Week 6 in MADRS total score was −13.5 with placebo compared to −17.1 with LATUDA (\(<0.01\))

- LATUDA was also superior to placebo in the key secondary measure of CGI-BP scores\(^2\)
SAFETY RESULTS

Adverse events and discontinuation rates for LATUDA vs placebo as monotherapy

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>LATUDA 20–60 mg/day (n=164)</th>
<th>LATUDA 80–120 mg/day (n=167)</th>
<th>Placebo (n=168)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>10.4%</td>
<td>17.4%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Headache</td>
<td>14.0%</td>
<td>9.0%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>7.9%</td>
<td>10.8%</td>
<td>2.4%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.3%</td>
<td>6.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Sedation</td>
<td>3.0%</td>
<td>7.2%</td>
<td>1.8%</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>6.1%</td>
<td>3.6%</td>
<td>4.2%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2.4%</td>
<td>6.0%</td>
<td>1.8%</td>
</tr>
<tr>
<td>EPS-related AEs*</td>
<td>4.9%</td>
<td>9.0%</td>
<td>2.4%</td>
</tr>
</tbody>
</table>

*Extrapyramidal symptoms (EPS) adverse events include drooling, dystonia, muscle rigidity, oromandibular dystonia, parkinsonism, torticollis, and trismus.

Discontinuation rates due to adverse events¹

- LATUDA 20–60 mg/day: 6.6%
- LATUDA 80–120 mg/day: 5.9%
- Placebo: 6.5%

Adverse events and discontinuation rates for LATUDA vs placebo as adjunctive therapy with lithium or valproate

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>Lithium/valproate + LATUDA (n=183)</th>
<th>Lithium/valproate + placebo (n=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>17.5%</td>
<td>11.0%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>8.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Tremor</td>
<td>8.2%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>7.7%</td>
<td>4.3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>7.1%</td>
<td>5.5%</td>
</tr>
<tr>
<td>EPS-related AEs*</td>
<td>15.3%</td>
<td>9.8%</td>
</tr>
</tbody>
</table>

*Extrapyramidal symptoms (EPS) adverse events include cogwheel rigidity, drooling, dystonia, globellar reflex, abnormal muscle rigidity, parkinsonism, tremor, and trismus.

Discontinuation rates due to adverse events²

- Lithium/valproate + LATUDA: 6%
- Lithium/valproate + placebo: 7.9%

IMPORTANT SAFETY INFORMATION FOR LATUDA

Neuroleptic Malignant Syndrome (NMS), a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy, intensive symptomatic treatment and medical monitoring, and treatment of any concomitant serious medical problems.

Please see additional Important Safety Information, including Boxed Warning, on back cover, and enclosed full Prescribing Information.
OBSERVED WEIGHT CHANGE OVER STUDY PERIOD

- A rank analysis of covariance (ANCOVA) model was used to compare weight changes from baseline among treatment groups during the study period.\(^1\)\(^2\)

**Weight change seen in all groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean endpoint change from baseline (kg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>LATUDA 20–60 mg/day</td>
<td>0.6</td>
<td>164</td>
</tr>
<tr>
<td>LATUDA 80–120 mg/day</td>
<td>0.0</td>
<td>167</td>
</tr>
<tr>
<td>Placebo</td>
<td>0.0</td>
<td>168</td>
</tr>
</tbody>
</table>

\(^*\)Last observation carried forward.

- The incidence of clinically significant weight gain (≥7% increase at endpoint) was 4.2% with LATUDA 20–60 mg/day, 0.7% with LATUDA 80–120 mg/day, and 0.7% with placebo.\(^1\)

- Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.\(^3\)

**Weight change seen in both groups**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mean endpoint change from baseline (kg)</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>lithium/valproate + LATUDA</td>
<td>0.2</td>
<td>183</td>
</tr>
<tr>
<td>lithium/valproate + placebo</td>
<td>0.1</td>
<td>163</td>
</tr>
</tbody>
</table>

\(^*\)Last observation carried forward.

- The incidence of clinically significant weight gain (≥7% increase at endpoint) was 3.1% with LATUDA and <1% with placebo.\(^2\)

- Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.\(^3\)

Please see Important Safety Information, including Boxed Warning, on back cover, and enclosed full Prescribing Information.
METABOLIC MEASURES

- A rank analysis of covariance (ANCOVA) model was used to analyze cholesterol, triglycerides, and glucose to compare changes from baseline among treatment groups.

**Minimal lipid and glucose changes with LATUDA vs placebo as monotherapy**

![Graph showing lipid and glucose changes from baseline (LOCF* endpoint)]

- Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.

**Minimal lipid and glucose changes with LATUDA vs placebo as adjunctive therapy**

![Graph showing lipid and glucose changes from baseline (LOCF* endpoint)]

- Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.
- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness.

*See Important Safety Information, including Boxed Warning, on back cover, and enclosed full Prescribing Information.*
Considerations, LATUDA should be prescribed in a manner that is most likely to minimize developing TD and the likelihood that it will become irreversible are believed to increase.

Tardive Dyskinesia (TD):
- Treatment of any concomitant serious medical problems.
- Concurrent therapy, intensive symptomatic treatment and medical monitoring, and management should include myoglobinuria (rhabdomyolysis), and acute renal failure. Management should include discontinuation of antipsychotic drugs, including LATUDA.

Neuroleptic Malignant Syndrome (NMS):
- Risk factors include older age, female gender, history of cerebrovascular disease, and concomitant use of anticholinergic medications.
- Management should include discontinuation of antipsychotic drugs, including LATUDA, and supportive care.

Adverse Reactions:
- Metabolic Changes:
  - Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing.
  - Dyslipidemia: Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Weight Gain: Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Hyperprolactinemia:
- As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

In the short-term, placebo-controlled monotherapy study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.1 ng/mL and was 1.5 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0.6% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

In the short-term, placebo-controlled adjunctive therapy with lithium or valproate study, the median change from baseline to endpoint in prolactin levels for LATUDA-treated females was 3.2 ng/mL and was 2.4 ng/mL for males. The proportion of female patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5x ULN was 0% for LATUDA-treated patients versus 0% for placebo-treated male patients.

Leukopenia, Neutropenia, and Agranulocytosis:
- Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug-induced leucopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

Orchestratic Hypotension and Syncope:
- LATUDA may cause orotachic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension.
- Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Sedation:
- The possibility of suicide attempt is inherent in psychiatric illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia:
- Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS
- Commonly observed adverse reactions (>5% incidence and at least twice the rate of placebo) for LATUDA were akathisia, extrapyramidal symptoms, and somnolence.

INDICATIONS
- LATUDA is indicated for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression) as monotherapy and as adjunctive therapy with lithium or valproate in adults.

Before prescribing LATUDA, please read the enclosed full Prescribing Information, including Boxed Warning.

References: