LURASIDONE IN THE TREATMENT OF SCHIZOPHRENIA: A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND OLANZAPINE-CONTROLLED STUDY

Herbert Y. Meltzer, Josephine Cucchiaro, Robert Silva, Masaaki Ogasa, Debra Phillips, Jane Xu, Amir H. Kalali, Edward Schweizer, Andrei Pikalov, Antony Loebel


INDICATION
LATUDA is indicated for the treatment of adult and adolescent patients (13 to 17 years) with schizophrenia.

IMPORTANT SAFETY INFORMATION FOR LATUDA
INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis.
STUDY OVERVIEW

Objective

- Evaluate the short-term efficacy and safety of LATUDA in the treatment of acute schizophrenia

Study design

- 6-week, randomized, multicenter, double-blind, placebo-controlled trial

- 478 patients were randomized to receive either a once-daily fixed dose of LATUDA 40 mg (n=120), LATUDA 120 mg (n=119), olanzapine 15 mg (n=123), or placebo (n=116)

- Olanzapine was included as an active control for assay sensitivity. This study was not designed for comparison of LATUDA to olanzapine

Dosing

- Patients assigned to receive LATUDA started treatment at their target dose; patients assigned to olanzapine received 10 mg/day for Days 1 to 7 and 15 mg/day thereafter

- Study medication was taken in the morning with a meal or after eating

Endpoints

- **Primary**: Change from baseline score in Positive and Negative Syndrome Scale (PANSS) total score at Week 6

- **Key secondary**: Change from baseline score in Clinical Global Impression-Severity (CGI-S) score at Week 6

Summary of results

- LATUDA 40 mg/day and 120 mg/day groups had statistically significant reductions in mean PANSS total score at Week 6 compared with placebo

- LATUDA resulted in statistically significant reductions in CGI-S score at Week 6 compared with placebo

- Discontinuation rates due to adverse events were relatively low in the LATUDA 40 mg/day (6.7%) and 120 mg/day (11.8%) groups and comparable to the placebo group (8.6%)

- LATUDA has a low potential for causing adverse weight and metabolic effects

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)

- In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. LATUDA is not approved for the treatment of patients with dementia-related psychosis
Efficacy Results

LATUDA 40 mg/day and 120 mg/day demonstrated statistically significant improvement in PANSS total score vs placebo

Primary endpoint: PANSS total score reductions (MMRM)*

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS mean change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>LATUDA 40 mg/day</td>
<td>-16.0</td>
</tr>
<tr>
<td>LATUDA 120 mg/day</td>
<td>-23.6†</td>
</tr>
<tr>
<td>Olanzapine 15 mg/day</td>
<td>-28.7§</td>
</tr>
</tbody>
</table>

This study was not designed for comparison of LATUDA to olanzapine. Olanzapine was included as an active control to assess assay sensitivity.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS mean change from baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>0</td>
</tr>
<tr>
<td>LATUDA 40 mg/day</td>
<td>-1.1</td>
</tr>
<tr>
<td>LATUDA 120 mg/day</td>
<td>-1.5¶</td>
</tr>
<tr>
<td>Olanzapine 15 mg/day</td>
<td>-1.5#</td>
</tr>
</tbody>
</table>

Statistically significant reductions were also seen in CGI-S score from baseline vs placebo

Key secondary endpoint: CGI-S score reductions (MMRM)†,‡

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## SAFETY AND TOLERABILITY

Treatment-emergent adverse events occurring with an incidence ≥5% (all causality)¹

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=116)</th>
<th>LATUDA 40 mg/day (N=119)</th>
<th>LATUDA 120 mg/day (N=118)</th>
<th>Olanzapine 15 mg/day (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>21.6%</td>
<td>21.8%</td>
<td>17.8%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>0.9%</td>
<td>11.8%</td>
<td>22.9%</td>
<td>7.4%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>4.3%</td>
<td>10.1%</td>
<td>15.3%</td>
<td>9.0%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>11.2%</td>
<td>12.4%</td>
<td>11.9%</td>
<td>10.7%</td>
</tr>
<tr>
<td>Sedation</td>
<td>3.4%</td>
<td>9.2%</td>
<td>13.6%</td>
<td>14.8%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>6.9%</td>
<td>10.1%</td>
<td>10.2%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Nausea</td>
<td>4.3%</td>
<td>10.9%</td>
<td>7.6%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Agitation</td>
<td>5.2%</td>
<td>11.8%</td>
<td>5.9%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>6.0%</td>
<td>7.6%</td>
<td>7.6%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Constipation</td>
<td>5.2%</td>
<td>5.0%</td>
<td>7.6%</td>
<td>6.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6.9%</td>
<td>4.2%</td>
<td>8.5%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Back pain</td>
<td>4.3%</td>
<td>5.0%</td>
<td>5.1%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1.2%</td>
<td>4.2%</td>
<td>5.1%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Restlessness</td>
<td>2.6%</td>
<td>5.9%</td>
<td>3.4%</td>
<td>3.3%</td>
</tr>
<tr>
<td>Salivary hypersecretion</td>
<td>0.0%</td>
<td>1.7%</td>
<td>6.8%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Musculoskeletal stiffness</td>
<td>1.7%</td>
<td>2.5%</td>
<td>5.1%</td>
<td>2.5%</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>1.2%</td>
<td>5.0%</td>
<td>0.8%</td>
<td>1.6%</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>3.4%</td>
<td>0.8%</td>
<td>2.5%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Weight increased</td>
<td>5.2%</td>
<td>1.7%</td>
<td>1.7%</td>
<td>20.3%</td>
</tr>
<tr>
<td>Toothache</td>
<td>5.2%</td>
<td>3.4%</td>
<td>2.5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>0.9%</td>
<td>1.7%</td>
<td>2.5%</td>
<td>9.8%</td>
</tr>
<tr>
<td>Psychotic disorder</td>
<td>6.9%</td>
<td>1.7%</td>
<td>3.4%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

**Extrapyramidal events**

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=116)</th>
<th>LATUDA 40 mg/day (N=119)</th>
<th>LATUDA 120 mg/day (N=118)</th>
<th>Olanzapine 15 mg/day (N=122)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parkinsonism</td>
<td>1.2%</td>
<td>9.2%</td>
<td>11.0%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Tremor</td>
<td>4.3%</td>
<td>1.7%</td>
<td>7.6%</td>
<td>5.7%</td>
</tr>
<tr>
<td>Dystonia</td>
<td>0.9%</td>
<td>3.4%</td>
<td>7.6%</td>
<td>0.8%</td>
</tr>
</tbody>
</table>

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### Changes in ECG with LATUDA

- In this study, the incidence of treatment-emergent ECG abnormalities in patients treated with LATUDA was comparable to those patients who received placebo¹

### Changes in prolactin with LATUDA

- The median change in prolactin from baseline to Week 6 (last observation carried forward [LOCF]) was –0.7 ng/mL with placebo, +0.7 ng/mL with LATUDA 40 mg/day, +4.5 ng/mL with LATUDA 120 mg/day, and +3.8 ng/mL with olanzapine 15 mg/day¹
- 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 compounds²

### IMPORTANT SAFETY INFORMATION FOR LATUDA

- Neuroleptic malignant syndrome (NMS) is a potentially fatal symptom complex reported with administration of antipsychotic drugs. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of antipsychotic drugs, including LATUDA, intensive symptomatic treatment and monitoring
METABOLIC PARAMETERS

Mean change in weight at Week 6 (LOCF)*

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\*LOCF=Last observation carried forward.

- Clinically significant weight gain (≥7% increase from baseline) occurred in the following groups:
  - 7.6% in patients receiving LATUDA 40 mg
  - 34.4% in patients receiving olanzapine 15 mg
  - 4.2% in patients receiving LATUDA 120 mg
  - 7.0% in patients receiving placebo

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

Mean change in lipid and glucose levels at Week 6 (LOCF)

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- 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

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IMPORTANT SAFETY INFORMATION AND INDICATION FOR LATUDA

INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS

Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Contraindications: 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)

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported with administration of antipsychotic drugs. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of treatment of patients with dementia-related psychosis.

Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes, including:
- 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 diabetes should be regularly monitored for worsening of glucose control; those with risk factors for diabetes should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.
- 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.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Monitor complete blood count in patients with a pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) or a history of drug-induced leukopenia/neutropenia. Discontinue LATUDA at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest at the beginning of treatment and when increasing dose. Monitor patients vulnerable to hypotension and those with cardiovascular and cerebrovascular disease.

Falls: Antipsychotics may cause somnolence, postural hypotension, or motor and sensory instability, which may lead to falls, causing fractures or other injuries. For patients with disease, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Use LATUDA with caution in patients who may experience conditions that increase body temperature (e.g., exercising strenuously, exposure to extreme heat, concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Antipsychotics, including LATUDA, have been associated with esophageal dysmotility and aspiration and should be used with caution in patients at risk for aspiration pneumonia.

Most Commonly Observed Adverse Reactions: The most commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:
- In adult patients: somnolence, akathisia, extrapyramidal symptoms, and nausea
- In adolescent patients (13 to 17 years): somnolence, nausea, akathisia, extrapyramidal symptoms (non-akathisia), vomiting, and rhinorrhea/rhinitis

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

INDICATION

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

References: