EFFECTIVENESS OF LURASIDONE IN PATIENTS WITH SCHIZOPHRENIA OR SCHIZOAFFECTIVE DISORDER SWITCHED FROM OTHER ANTIPSYCHOTICS: A RANDOMIZED, 6-WEEK, OPEN-LABEL STUDY

Joseph P. McEvoy, Leslie Citrome, David Hernandez, Josephine Cucchiaro, Jay Hsu, 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.

Please see additional Important Safety Information, including Boxed Warning, on back cover, and enclosed full Prescribing Information.
STUDY OVERVIEW

Objective

• Examine the effectiveness of switching patients to LATUDA using 3 different dosing strategies

Study design

• Adult patients who had insufficient efficacy and/or safety or tolerability concerns on their current antipsychotic medication were randomized into an open-label, parallel-group, 6-week study (n=240). At screening, patients fulfilled DSM-IV criteria for a primary diagnosis of schizophrenia or schizoaffective disorder, and had a duration of illness ≥1 year

*4 patients were randomized but exited the study before receiving LATUDA.

Dosing

• All patients assigned to receive LATUDA underwent 1 of 3 titration dosing schedules for 2 weeks, before flexible dosing:
  – LATUDA 40 mg/day: Days 1 to 14
  – LATUDA 40 mg/day: Days 1 to 7; LATUDA 80 mg/day: Days 8 to 14
  – LATUDA 80 mg/day: Days 1 to 14

• Patients’ preswitch antipsychotic dose was tapered by 50% by Day 7, followed by complete discontinuation at Day 14

• Flexible dosing of LATUDA within the dosing range of 40–120 mg/day was permitted after Day 14

• LATUDA was taken once daily in the evening, with a meal or within 30 minutes after eating

Endpoints

• Primary endpoint: Time to treatment failure defined as any occurrence of insufficient clinical response, exacerbation of underlying illness, or discontinuation due to adverse events

• Secondary endpoints included: Safety and tolerability, Positive and Negative Syndrome Scale (PANSS) total score, and Clinical Global Impression-Severity Scale (CGI-S) score

Summary of results

• Switching adult patients with schizophrenia to LATUDA from a variety of antipsychotic agents was successfully accomplished with any of the 3 dosing strategies employed in this trial

• 82.5% completion rate among patients receiving LATUDA
  – 7.9% treatment failure rate among patients receiving LATUDA

• No clinically meaningful differences in treatment failure, adverse reactions, metabolic changes, or efficacy among the 3 dosing strategies were noted

• When switching to LATUDA, statistically significant symptom improvement was seen in PANSS total score and CGI-S score

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

Over 80% of patients completed treatment*1

Treatment failure Prospectively defined as any of the following:
• Insufficient clinical response: 1.3%
• Discontinuation due to adverse event: 6.7%
  – Exacerbation of underlying disease: 1.7%

Lost to follow-up 3.8%
Other† 5.8%
Treatment failure 7.9%

Lost to follow-up 3.8%
Completed treatment 82.5%

*4 patients were randomized but exited the study before receiving LATUDA.
†Other includes: protocol violation, non-compliance, administrative reason, investigator decision, withdrew consent.

Primary endpoint: Time to treatment failure

No statistically significant differences in time to treatment failure among 3 treatment groups

LATUDA monotherapy

Taper previous antipsychotic
EFFICACY RESULTS

Secondary endpoint: change in PANSS total score with LATUDA (LOCF)*

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
<th>LOCF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Latuda 40/40</td>
<td>Latuda 40/80</td>
<td>Latuda 80/80</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>−10</td>
<td>−8</td>
<td>−6</td>
<td>−4</td>
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</table>

• Results were similar regardless of switch strategy. Switch strategy may be based on individual need and clinical judgment1

• LATUDA also improved CGI-S scores, a secondary outcome, at Week 6 (LS mean change −0.2 from baseline [LOCF]).
  Baseline CGI-S score for all patients receiving LATUDA (all subjects) was 3.7 (n=235)1

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.

• The risk of developing tardive dyskinesia (TD), a syndrome of abnormal involuntary movement, 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.
SAFETY AND TOLERABILITY

Adverse reactions occurring in ≥5% of all patients

<table>
<thead>
<tr>
<th>Adverse reaction</th>
<th>LATUDA 40/40 (n=72)</th>
<th>LATUDA 40/80 (n=87)</th>
<th>LATUDA 80/80 (n=81)</th>
<th>All LATUDA (n=240)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>13.9%</td>
<td>9.2%</td>
<td>18.5%</td>
<td>13.8%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.2%</td>
<td>18.4%</td>
<td>14.8%</td>
<td>12.9%</td>
</tr>
<tr>
<td>Akathisia</td>
<td>8.3%</td>
<td>14.9%</td>
<td>13.6%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Headache</td>
<td>9.7%</td>
<td>11.5%</td>
<td>7.4%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5.6%</td>
<td>6.9%</td>
<td>8.6%</td>
<td>7.1%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>9.7%</td>
<td>8.0%</td>
<td>2.5%</td>
<td>6.7%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>4.2%</td>
<td>10.3%</td>
<td>2.5%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

METABOLIC PARAMETERS

Change in metabolic parameters in all patients (LOCF)

- **WEIGHT CHANGE (n=220)**
  - Mean change from baseline (kg): -0.3
  - Median change from baseline (-0.66 lb)

- **TOTAL CHOLESTEROL (n=219)**
  - Median change from baseline: -1.0

- **TRIGLYCERIDES (n=219)**
  - Median change from baseline: -6.0

- **GLUCOSE (n=219)**
  - Median change from baseline: -1.0

- Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.
- 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 antipsychotic drugs, including LATUDA, intensive symptomatic treatment and monitoring.

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).

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