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


Introduction
The efficacy of Latuda® (lurasidone HCl) was established in five 6-week, double-blind, placebo-controlled studies in adult patients with schizophrenia. This open-label study, which was not one of these five studies, was conducted to evaluate the effectiveness of switching adult patients with schizophrenia to LATUDA from a variety of antipsychotics using 3 different dosing strategies.

Summary
The primary outcome was time to treatment failure, defined as insufficient clinical response, exacerbation of underlying illness, or discontinuation due to adverse reaction. Secondary outcomes included the following assessments: safety and tolerability, Positive and Negative Syndrome Scale (PANSS) total score, and Clinical Global Impression-Severity Scale (CGI-S) score.1

<table>
<thead>
<tr>
<th>Completed treatment</th>
<th>Treatment failure</th>
<th>Lost to follow-up</th>
<th>Other†</th>
</tr>
</thead>
<tbody>
<tr>
<td>82.5%</td>
<td>7.9%</td>
<td>3.8%</td>
<td>5.8%</td>
</tr>
</tbody>
</table>

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

Adverse reactions occurring in ≥5% of all LATUDA patients were nausea (13.8%), insomnia (12.9%), akathisia (12.5%), headache (9.6%), vomiting (7.1%), somnolence (6.7%), and dry mouth (5.8%).

INDICATION AND USAGE
LATUDA is indicated for the treatment of patients with schizophrenia. Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-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.

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 use in patients with dementia-related psychosis.

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

Dosing strategies for 6-week, open-label study*1

- LATUDA 40 mg/day
- LATUDA 80 mg/day

Taper previous antipsychotic dose

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

- Similar results were achieved regardless of switch strategy:
  - Switch strategies utilized a gradual cross-taper to switch symptomatic patients from other antipsychotics to LATUDA 40 mg/day or 80 mg/day.
- The effect of LATUDA on safety parameters was evaluated, and the safety profile was consistent with results from controlled 6-week studies in adult patients with schizophrenia.
- Symptom improvement was seen over the course of the 6-week study.

- Study patients (n=240) were switched from a variety of antipsychotic agents: quetiapine (25.8%), risperidone (21.3%), aripiprazole (18.3%), ziprasidone (11.3%), olanzapine (10.0%), paliperidone (3.8%), perphenazine or fluphenazine (2.9%), haloperidol (2.5%), iloperidone (1.7%), chlorpromazine (1.3%), asenapine (0.8%), thiothixene (0.4%).

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PRIMARY OUTCOME ASSESSMENT: TIME TO TREATMENT FAILURE

Completion rate and treatment failure rate among patients receiving LATUDA at week 6 (n=240)*1

- **82.5%** Completed treatment
- **3.8%** Lost to follow-up
- **5.8%** Other†
- **7.9%** Treatment failure

Prospectively defined as any of the following:
- Insufficient clinical response: 1.3%
- Discontinuation due to adverse event: 6.7%, including:
  - Exacerbation of underlying disease: 1.7%

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

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)

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PRIMARY OUTCOME ASSESSMENT: TIME TO TREATMENT FAILURE

Time to discontinuation due to treatment failure (n=240)**†

<table>
<thead>
<tr>
<th>Days from start of study drug</th>
<th>Probability of treatment failure (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>4</td>
<td>10%</td>
</tr>
<tr>
<td>6</td>
<td>15%</td>
</tr>
<tr>
<td>8</td>
<td>20%</td>
</tr>
<tr>
<td>10</td>
<td>25%</td>
</tr>
<tr>
<td>12</td>
<td>30%</td>
</tr>
<tr>
<td>14</td>
<td>35%</td>
</tr>
<tr>
<td>16</td>
<td>40%</td>
</tr>
<tr>
<td>18</td>
<td>45%</td>
</tr>
<tr>
<td>20</td>
<td>50%</td>
</tr>
<tr>
<td>22</td>
<td>55%</td>
</tr>
<tr>
<td>24</td>
<td>60%</td>
</tr>
<tr>
<td>26</td>
<td>65%</td>
</tr>
<tr>
<td>28</td>
<td>70%</td>
</tr>
<tr>
<td>30</td>
<td>75%</td>
</tr>
<tr>
<td>32</td>
<td>80%</td>
</tr>
<tr>
<td>34</td>
<td>85%</td>
</tr>
<tr>
<td>36</td>
<td>90%</td>
</tr>
<tr>
<td>38</td>
<td>95%</td>
</tr>
<tr>
<td>40</td>
<td>100%</td>
</tr>
</tbody>
</table>

- LATUDA 40/40 (n=5/72)
- LATUDA 40/80 (n=8/87)
- LATUDA 80/80 (n=6/81)

*4 patients were randomized but exited the study before receiving LATUDA.
†Treatment failure was defined as insufficient clinical response, exacerbation of underlying disease, or an adverse event.

- 19 patients (79%) discontinued due to treatment failure

IMPORTANT SAFETY INFORMATION FOR LATUDA

Cerebrovascular Adverse Reactions, Including Stroke: 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.

Neuroleptic Malignant Syndrome (NMS): 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.
SAFETY RESULTS

### Adverse reactions occurring in ≥5% of all patients*1

<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>

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

### Metabolic changes

#### Change in metabolic parameters in all patients (LOCF)1,2

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Change from baseline (kg)</th>
<th>Median change from baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Weight (n=220)</td>
<td>-0.3 (-0.66 lb)</td>
<td>-0.1</td>
</tr>
<tr>
<td>Total Cholesterol (n=219)</td>
<td>-1.0</td>
<td>-6.0</td>
</tr>
<tr>
<td>Triglycerides (n=219)</td>
<td>-1.0</td>
<td></td>
</tr>
<tr>
<td>Glucose (n=219)</td>
<td>-1.0</td>
<td></td>
</tr>
</tbody>
</table>

LOCF = Last observation carried forward.

- Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended3
- Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics3
- Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia, including polydipsia, polyuria, polyphagia, and weakness3

### Change in prolactin

- Median change from baseline in prolactin (LOCF) through study endpoint for all patients after switching to LATUDA was 0.5 ng/mL (n=219)2
- As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds3

Please see additional Important Safety Information, including Boxed Warning, on back cover, and enclosed full Prescribing Information.
Tardive Dyskinesia (TD): TD is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients with antipsychotic drugs. There is no known treatment for established cases of TD, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

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

- In addition, LATUDA improved CGI-S scores, a secondary endpoint, 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).
CONCLUSIONS

- 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.
- No clinically meaningful differences in treatment failure, adverse reactions, metabolic changes, or efficacy among the 3 dosing strategies were noted.
- Adverse reactions occurring in ≥5% of all LATUDA patients were nausea (13.8%), insomnia (12.9%), akathisia (12.5%), headache (9.6%), vomiting (7.1%), somnolence (6.7%), and dry mouth (5.8%).
- 82.5% completion rate among all patients receiving LATUDA.
- 79% treatment failure rate among patients receiving LATUDA.
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WARNINGS AND PRECAUTIONS

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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 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 during treatment with atypical antipsychotics 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 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 leukopenia/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.

Orchietomy and Sympathetic: LATUDA may cause orthostatic hypotension. Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension and in patients with known cardiovascular disease or cerebrovascular disease.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold (e.g., Alzheimer’s dementia).

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: 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.

Suicide: The possibility of suicide attempt is inherent in psychotic 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 somnolence, akathisia, extrapyramidal symptoms, and nausea.

INDICATION

LATUDA is indicated for the treatment of schizophrenia in adults.

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

REFERENCES


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