Lurasidone: A New Antipsychotic For Schizophrenia

Theodore Pikoulas, PharmD
PGY2 Psychiatric Pharmacy Resident
Louis Stokes Cleveland VAMC

Objectives
• Review the pharmacology and the pharmacokinetics
• Identify the indications, dosing, and administration
• Assess the safety
• Examine recent changes to package insert

Introduction
• New second-generation atypical antipsychotic
• Approved by the FDA in October 2010
• No conflicts of interest to report

Mechanism of Action
• Exact mechanism of action is unknown
• Antagonistic effects on dopamine (D2) and serotonin (SHT2a) receptors
• Greater affinity for:
  ◦ SHT2a
  ◦ Alpha2c-adrenergic
• Highest affinity for the SHT2 receptor subtype than any other medication in its class

Pharmacology/Pharmacokinetics
• Low affinity:
  ◦ Alpha1-adrenergic receptors
• Almost no affinity for:
  ◦ Histamine H1 receptors
  ◦ Muscarinic M1 receptors
• Suggesting a reduced potential for:
  ◦ Orthostasis
  ◦ Weight gain
  ◦ Sedation

Ishibashi T. JPET 2010.
Other Effects?

- Cognitive Effects
  - 5HT₇
  - 5HT₁₄
  - Alpha₂c
- Antidepressant and Anxiolytic Effects
  - 5HT₇
  - 5HT₁₄
  - Sleep
  - 5HT₇

Pharmacokinetic Properties

- Peak concentrations (Tmax) in 1-3 hours
- t½ about 18 hours
- Highly plasma protein bound (99.8%)
- Metabolized mainly in the liver by CYP3A4
- ID-14283:
  - Main active metabolite
  - Comparable pharmacological profile
  - Shorter life (7.48-10 hours) than lurasidone

Indications & Dosing/Administration

- FDA-Approved Indications
  - Treatment of patients with acute schizophrenia
  - Efficacy has not been established in controlled studies for more than 6 weeks
  - Should periodically re-evaluate the long-term usefulness of the drug for the individual patient

Potential Off-Label Uses

- Schizoaffective disorder
- Bipolar disorder
- Chronic maintenance treatment of schizophrenia
- Currently being evaluated for the use in bipolar depression
  - PREVAIL 1, 2, 3
  - Monotherapy, add-on therapy, and prophylaxis

Dosing

- Starting dose = 40 mg/daily
- Dosage range = 40 mg/day-160 mg/day
- Moderate and severe renal impairment should not exceed 80 mg/day
  - Hepatic impairment:
    - Moderate – should not exceed 80 mg/day
    - Severe – should not exceed 40 mg/day
Administration

- Absorption estimated at 9-19%
  - Dose-dependent
- A meal over 350 calories will:
  - Increase the mean Cmax about 3-times
  - Increase AUC about 2-times
- Important to provide patient counseling

Safety

Adverse Effects

- Commonly Observed Adverse Reactions
  - Somnolence
  - Akathisia
  - Nausea
  - Parkinsonism

<table>
<thead>
<tr>
<th></th>
<th>Placebo (%)</th>
<th>Lurasidone 20mg/day (%)</th>
<th>Lurasidone 40mg/day (%)</th>
<th>Lurasidone 80mg/day (%)</th>
<th>Lurasidone 120mg/day (%)</th>
<th>Lurasidone 160mg/day (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>9</td>
<td>10</td>
<td>21</td>
<td>23</td>
<td>39</td>
<td>20</td>
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<tr>
<td>All EPS events, excluding akathisia/ restlessness</td>
<td>7</td>
<td>6</td>
<td>14</td>
<td>13</td>
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<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>7</td>
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<tr>
<td>Dystonia</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
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<tr>
<td>Parkinsonism</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
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<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
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</tbody>
</table>

Weight Changes Vs. Placebo

- Mean change in weight (kg) from baseline:
  - Placebo = - 0.02 kg
  - Lurasidone:
    - 20 mg/day = - 0.15 kg
    - 40 mg/day = 0.22 kg (~ 0.5 lbs)
    - 80 mg/day = 0.54 kg (~ 1.2 lbs)
    - 120 mg/day = 0.68 kg (~ 1.5 lbs)
    - 160 mg/day = 0.60 kg (~ 1.3 lbs)

Lipid Changes Vs. Placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo = - 5.8</th>
<th>Lurasidone = - 13.4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Cholesterol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo</td>
<td>- 20 mg/day</td>
<td>20 mg/day</td>
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<tr>
<td></td>
<td>- 40 mg/day</td>
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<td></td>
<td>- 80 mg/day</td>
<td>80 mg/day</td>
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<td>- 120 mg/day</td>
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<td>- 160 mg/day</td>
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<tr>
<td>Triglycerides</td>
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</tr>
<tr>
<td>Placebo</td>
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<tr>
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<td>- 120 mg/day</td>
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<tr>
<td></td>
<td>- 160 mg/day</td>
<td>160 mg/day</td>
</tr>
</tbody>
</table>
### Glucose Changes Vs. Placebo

- **Mean change from baseline (mg/dL):**
  - Placebo = 0
  - Lurasidone:
    - 20 mg/day = -0.6
    - 40 mg/day = 2.6
    - 80 mg/day = -0.4
    - 120 mg/day = 2.5
    - 160 mg/day = 2.5

### QTc Prolongation

- No post-baseline QTc prolongations exceeding 500 msec were reported
- No cases of torsade de pointes
- QTc prolongation evaluated in a study:
  - 87 clinically stable patients
  - Patients treated with lurasidone 120mg, 600mg, or ziprasidone 160mg daily
  - No lurasidone treated patients experienced QTc increases greater than 60 msec from baseline.

### Drug Interactions

<table>
<thead>
<tr>
<th>Coadministered Drug</th>
<th>Lurasidone dose</th>
<th>Effect on Lurasidone Cmax</th>
<th>Effect on Lurasidone AUC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketoconazole (strong CYP3A4 inhibitor) 400mg/day x 5 days</td>
<td>10mg single dose</td>
<td>6.9-times lurasidone alone</td>
<td>9-times lurasidone alone</td>
</tr>
<tr>
<td>Diltiazem (moderate CYP3A4 inhibitor) 240mg/day x 5 days</td>
<td>20mg single dose</td>
<td>2.1-times lurasidone alone</td>
<td>2.3-times lurasidone alone</td>
</tr>
<tr>
<td>Rifampin (strong CYP3A4 inducer) 600mg/day x 8 days</td>
<td>40mg single dose</td>
<td>1/7th of lurasidone alone</td>
<td>1/5th of lurasidone alone</td>
</tr>
<tr>
<td>Lithium 600mg BID x 8 days</td>
<td>120mg/day x 8 days</td>
<td>0.9-times lurasidone alone</td>
<td>1.1-times lurasidone alone</td>
</tr>
</tbody>
</table>

**Recommendation**

- Should not be coadministered with lurasidone
- Lurasidone dose should not exceed 80 mg/day if coadministered
- Should not be coadministered with lurasidone
- No dose adjustment required

### Conclusions/Summary

**Potential Advantages:**
- Well tolerated and favorable metabolic profile
- No signs of glucose elevation or lipid changes
- Small increase in weight gain
- Good cardiovascular tolerability
- No hypotension
- No widening the QT interval
- Once daily dosing, no initial dose titration

**Potential Disadvantages:**
- Lacks long-term efficacy trials
- Side effects
  - Dose dependent EPS
- Cost of medication
  - $18.46 a tablet
  - $6,737.90 per year
- Must be taken with a meal over 350 calories
- No comparative studies

### References

References


Question 1

- Lurasidone has higher affinity that any other medication in its class for what receptor subtype?
  A. M₁
  B. 5HT₇
  C. 5HT₂a
  D. H₁
  E.

  Answer: B

Question 2

- Lurasidone is currently marketed as 40, 80, and 120 mg strength tablets?
  A. True
  B. False

  Answer: B

Question 3

- Lurasidone is FDA-approved for what indication?
  A. Bipolar Mania
  B. Bipolar Depression
  C. Schizoaffective Disorder
  D. Acute Schizophrenia

  Answer: D

Question 4

- Lurasidone should be administered with a meal over 350 calories?
  A. True
  B. False

  Answer: A