Major depressive episodes associated with bipolar I disorder (bipolar depression) can be difficult to diagnose, which can prove challenging for clinicians and frustrating for patients. Many patients wait 10 years or longer from the time of symptom onset to an accurate diagnosis.1,2 According to one study, patients undergo a mean of 3.5 diagnoses and see 4 health care professionals before finally receiving a diagnosis of bipolar disorder.3

Misdiagnosis is a frequent challenge. In a study of patients in a community sample who screened positive for bipolar disorder, nearly half (49%) had previously received no diagnosis, and nearly a third (31.2%) had received an incorrect diagnosis of major depressive disorder. Only 19.8% received a diagnosis of bipolar disorder.3 Consistent with this finding, unipolar depression, at 60%, is the most common misdiagnosis among patients later diagnosed with bipolar disorder. Anxiety disorder is the second most common misdiagnosis, at 26%.1

One difficulty in diagnosing bipolar disorder is that affected patients are more likely to present with depressive symptoms than with manic symptoms,4 and over the long-term course of the disease, they typi-
Jane is a 30-year-old elementary school teacher who has been referred to a new psychiatrist by her primary care physician after she expressed frustration with her lack of response to antidepressant therapy. When asked how she is doing in general, she responds that this year has been tough. When urged for specifics, Jane divulges that she has experienced on-and-off bouts of depression for about 10 years. Jane complains that she has low energy and has had increasing difficulty coping with the demands of her job, which she used to love. Part of Jane’s frustration with her previous psychiatrist is that she is tired of trying one antidepressant after another.

Jane’s new psychiatrist uses the Patient Health Questionnaire–9 item (PHQ-9) to screen her for depression and the Mood Disorder Questionnaire (MDQ) to screen for a lifetime history of mania. The results of the MDQ point to a history of manic episodes, but more information is required. The psychiatrist conducts a full diagnostic interview with Jane to come to a definitive diagnosis. Though Jane denies feeling “unusually good” in the past, the psychiatrist decides to speak with Jane’s husband to gather collateral information to supplement the full diagnostic interview. Jane’s husband reveals that Jane has had several periods of unusual behavior in the past, during which time she was uncharacteristically short tempered and jeopardized the couple’s finances with impulsive decisions. On the basis of the PHQ-9, the MDQ, the full diagnostic interview, and collateral information, Jane’s psychiatrist diagnoses her with bipolar I disorder and initiates therapy with a mood stabilizer.

Jane returns a month after she started taking the mood stabilizer. Although she reports that she is adherent, which is confirmed by plasma levels that the psychiatrist ordered, she complains that she is finding little enjoyment in her daily activities.

The psychiatrist keeps Jane on the mood stabilizer, and after discussing all available treatment options with her, decides to add Latuda® (lurasidone HCl) for the treatment of her major depressive episodes associated with bipolar I disorder (bipolar depression).

LATUDA: A Treatment Option for Bipolar Depression
The efficacy of LATUDA for the adjunctive treatment of bipolar depression was evaluated in a phase 3, randomized, multicenter, double-blind, placebo-controlled clinical trial of 348 patients with bipolar I disorder. The results of this pivotal trial were published in the February 2014 issue of The American Journal of Psychiatry. All psychotropic medications other than lithium or valproate were tapered off during the screening phase, and a therapeutic range of lithium (0.6-1.2 mEq/L) or valproate (50-125 μg/mL) was maintained for at least 28 days. The patients were then randomized to receive flexibly dosed adjunctive LATUDA 20 mg/day to 120 mg/day plus lithium or valproate (n=183) or placebo plus lithium or valproate (n=165) for 6 weeks. Study medication was taken once daily in the evening by mouth with a meal (eg, dinner) or within 30 minutes after eating.

Short-term Efficacy
Figure 1 shows the improvement in depressive symptoms for the LATUDA and placebo groups from baseline to Week 6 as measured using the Montgomery-Åsberg Depression Rating Scale (MADRS) total score, which was the study’s primary efficacy endpoint. The MADRS is a 10-item, clinician-rated scale with total scores ranging from 0 to 60. At Week 6, LATUDA added to lithium or valproate was associated with statistically significantly greater reduction from baseline MADRS total score than was placebo added to lithium or valproate (P<.01). Latuda® (lurasidone HCl)
compared with a mean decrease of 0.9 mg/dL for patients who received placebo. Total cholesterol concentration decreased by a mean of 3.1 mg/dL in the LATUDA group versus a decrease of 2.9 mg/dL in the placebo group. The mean triglyceride concentration increased by 4.6 mg/dL in the LATUDA group and decreased by 4.6 mg/dL in the placebo group.

In these 2 studies, the median prolactin concentration increased by 2.8 ng/mL between baseline and Week 6 for patients in the LATUDA group and remained unchanged for patients in the placebo group. For male patients, the change from baseline to Week 6 was +2.4 ng/mL with LATUDA and −0.1 ng/mL with placebo; for female patients, the median change from baseline was +3.2 ng/mL with LATUDA versus +0.4 ng/mL with placebo.

Extrapyramidal symptoms (EPS), akathisia, and tardive dyskinesia were examined using the Simpson-Angus Scale, the Barnes Akathisia Scale (BAS), and the Abnormal Involuntary Movement Scale (AIMS), respectively. A shift from normal at baseline to abnormal at Week 6 (or at last observation carried forward for patients who discontinued prematurely) was noted for 2.8% of patients who received LATUDA plus lithium or valproate versus 2.1% of patients receiving placebo plus lithium or valproate. On the BAS, worsening from baseline to endpoint was noted for 8.7% versus 2.1% of patients who received LATUDA or placebo, respectively, whereas on the AIMS, worsening from baseline was noted for 2.8% of patients who received LATUDA versus 0.6% of those receiving placebo. EPS observed during the 6-week study included akathisia (11% vs 5% for LATUDA and placebo groups, respectively), dystonia (1% vs <1%), parkinsonism (13% vs 8%), and restlessness (4% vs <1%).

**Longer-term Safety**

Patients with bipolar depression who completed the two 6-week trials of Latuda® (lurasidone HCl) as adjunctive therapy with lithium or valproate were eligible to continue into a 6-month, uncontrolled, open-label, flexible-dose extension study. Eligible patients who received placebo in the...

*Abbreviations: Li, lithium; LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; VPA, valproate.*

**Figure 1. Primary Efficacy Endpoint: MADRS Score**

Comparing placebo with LATUDA (20-120 mg) in adjunctive therapy, there is a significant reduction in the MADRS score from baseline to Week 6, indicating improvement in depressive symptoms. The effect size is 0.34, indicating a moderate effect.

*P<.05; **P<.01; ***P<.001.

Compared with placebo, LATUDA (20-120 mg) showed a significant improvement in depressive symptoms as measured by the MADRS score.

**Figure 2. Adverse Reactions in >2% of LATUDA-Treated Patients and at Greater Incidence Than Placebo**

<table>
<thead>
<tr>
<th>Adverse Reaction</th>
<th>LATUDA 20-120 mg + Li/VPA (N=360)</th>
<th>Placebo + Li/VPA (N=334)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>14</td>
<td>9</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Somnolence</td>
<td>14</td>
<td>11</td>
</tr>
<tr>
<td>Akathisia</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Increased Appetite</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Weight Increased</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Abbreviations: EPS, extrapyramidal symptoms; Li, lithium; VPA, valproate. Note: Figures rounded to the nearest integer.

*EPS includes bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.

†Somnolence includes adverse event terms: hypersomnia, hypersomnolence, sedation, and somnolence.

The effectiveness of LATUDA for longer-term use—that is, for more than 6 weeks—has not been established in controlled studies.

Please see Brief Summary of full Prescribing Information, including Boxed Warning, on page S5.
AN EXPERT’S PERSPECTIVE

Case Commentary by Henry A. Nasrallah, MD

The case of Jane* illustrates several important features of bipolar depression that are well recognized by psychiatrists. First, her depressive symptoms began at age 20; and early-onset depression strongly suggests bipolar disorder rather than unipolar depression. Second, Jane experienced unsuccessful trials with various antidepressants. This is quite common in the history of patients with bipolar disorder who are frequently misdiagnosed as having major depressive disorder. Third, Jane is not enjoying her teaching job anymore and reports low energy and impaired coping, all suggesting persistent depression.

The new psychiatrist suspects that Jane may have bipolar depression and inquires about past manic episodes, which Jane denies. However, as a testament to the value of informants in psychiatric practice, her husband clearly describes episodes of aggressiveness, impulsivity, and risky behavior that threatened the household financial integrity. Short-term studies were switched to LATUDA in the longer-term extension study. Adverse events that occurred in at least 5% of patients who continued on LATUDA adjunctive therapy plus lithium or valproate (n=254) included parkinsonism (14.2%), somnolence (9.1%), akathisia (8.7%), insomnia (7.1%), nausea (5.5%), and headache (5.5%). Changes in weight and laboratory parameters from open-label baseline to Week 24 were as follows: mean change in weight, 1.7 pounds; mean change in glucose, −0.5 mg/dL; mean change in cholesterol, 0.4 mg/dL; mean change in triglycerides, 1.6 mg/dL; and median change in prolactin levels, −1.3 ng/mL.¹

This fourth clue underscores the fact that bipolar manic episodes do not always manifest in euphoria, but can display other core symptoms of mania such as impulsivity, aggressiveness, and risky behavior that are deviations from one’s usual baseline. Fifth, even when treated with a mood stabilizer at therapeutic serum levels, Jane continues to experience depressive symptoms, confirming data showing that depression as a mood state dominates the symptomatic days of bipolar disorder.¹

Finally, Jane’s new psychiatrist makes the clinical decision to add an FDA-approved medication for the treatment of major depressive episodes associated with bipolar I disorder (bipolar depression).

References

*Hypothetical case representing a fictional patient.
INDICATIONS AND USAGE
LATUDA is indicated for:
- Treatment of adult and adolescent patients age 13 to 17 years with depressive episodes associated with bipolar I disorder (bipolar depression).
- Adjunctive treatment with lithium or valproate in adult patients with major depressive episodes associated with bipolar I disorder (bipolar depression).

CONTRAINDICATIONS
- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
- Strong CYP3A4 inhibitors (e.g., ketoconazole, clarithromycin, ritonavir, and voriconazole, mibefradil, etc.).
- Strong CYP3A4 inducers (e.g., rifampin, avaslimbe, St. John’s wort, phenytoin, carbamazepine, etc.).

WARNINGS AND PRECAUTIONS
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. Analyses of 17 placebo-controlled trials (modal duration of 10 weeks), largely in patients taking atypical antipsychotic drugs, revealed a risk of death in drug-treated patients of 1.5-2.3 times the risk of death in placebo-treated patients. Over the course of a typical 10-week controlled trial, the rate of death in drug-treated patients was about 4.5%, compared to a rate of about 2.6% in the placebo group. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature. Observational studies suggest that, similar to atypical antipsychotic drugs, treatment with conventional antipsychotic drugs may increase mortality. The extent to which the findings of increased mortality in observational studies may be attributed to the antipsychotic drug as opposed to some characteristic(s) of the patient is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
In pooled analyses of placebo-controlled trials of antipsychotic drugs (SSRIs and other antidepressant classes) that included approximately 77,000 children, adolescents, and young adult patients, the incidence of suicidal thoughts and behaviors in pediatric and young adult patients was greater in antidepressant-treated patients than in placebo-treated patients. The drug-placebo differences in the number of cases of suicidal thoughts and behaviors per 1000 patients treated are provided in Table 1. No suicides occurred in any of the pediatric studies. There were suicides in the adult studies, but the number was not sufficient to reach any conclusion about antipsychotic drug effect on suicide.

Table 1: Risk Differences of the Number of Cases of Suicidal Thoughts or Behaviors in the Pooled Placebo-Controlled Trials of Antidepressants in Pediatric and Adult Patients

<table>
<thead>
<tr>
<th>Age Range</th>
<th>Drug-Placebo Difference in Number of Patients of Suicidal Thoughts or Behaviors per 1000 Patients Treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;18</td>
<td>Increases Compared to Placebo 14 additional patients</td>
</tr>
<tr>
<td>18-24</td>
<td>5 additional patients</td>
</tr>
<tr>
<td>25-64</td>
<td>Decreases Compared to Placebo 1 fewer patient</td>
</tr>
<tr>
<td>≥65</td>
<td>6 fewer patients</td>
</tr>
</tbody>
</table>

LATUDA is not approved for use in pediatric patients with depression.

It is unknown whether the risk of suicidal thoughts and behaviors in pediatric and young adult patients extends to longer-term use, i.e., beyond four months. However, there is substantial evidence from placebo-controlled maintenance studies in adults with MDD that antidepressants delay the recurrence of depression.

Monitor all antidepressant-treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the health care provider. Consider changing the therapeutic regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who are experiencing emerging suicidal thoughts or behaviors.

Cerebrovascular Adverse Reactions, Including Stroke in Elderly Patients with Dementia-Related Psychosis
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
A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including LATUDA.

Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure.

The diagnostic evaluation of patients with this syndrome is complicated. It is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology.

The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for NMS.

If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. If reintroduced, the patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia
Tardive dyskinesia is a syndrome consisting of potentially irreversible, involuntary, dyskinetic movements that can develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

The risk of developing tardive dyskinesia 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.

There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and thereby may possibly mask the underlying process. The effect that symptomatic suppression has on the long-term course of the syndrome is unknown.

Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically.

If signs and symptoms of tardive dyskinesia appear in a patient on LATUDA, drug discontinuation should be considered. However, some patients may require treatment with LATUDA despite the presence of the syndrome.
Metabolic Changes
Atypical antipsychotic drugs have been associated with metabolic changes that may increase cardiovascular/cerebrovascular risk. These metabolic changes include hyperglycemia, dyslipidemia, and body weight gain. While all of the drugs in the class have been shown to produce some metabolic changes, each drug has its own specific risk profile.

Hyperglycemia and Diabetes Mellitus
Hyperglycemia, in some cases, can be extreme and associated with ketoadiabeticosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics. Because LATUDA was not marketed at the time these studies were performed, it is not known if LATUDA is associated with this increased risk.

Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. 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 treatment 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.

Schizophrenia

Adults
Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 2.

Table 2: Change in Fasting Glucose in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo 20 mg/day</th>
<th>LATUDA 20-60 mg/day</th>
<th>LATUDA 80-120 mg/day</th>
<th>LATUDA 120-160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Patients with shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>8.3% (52/628)</td>
<td>11.7% (7/60)</td>
<td>12.7% (57/449)</td>
<td>6.8% (32/472)</td>
</tr>
<tr>
<td>Proportion of patients with glucose (≥ 126 mg/dL)</td>
<td>10.0% (8/80)</td>
<td>10.0% (7/70)</td>
<td>10.0% (41/410)</td>
<td>5.6% (6/108)</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in glucose of +1.8 mg/dL at week 24 (n=355), +0.8 mg/dL at week 36 (n=299) and +2.3 mg/dL at week 52 (n=307). Adolescents

In studies of adolescents and adults with schizophrenia, changes in fasting glucose were similar. In the short-term, placebo-controlled study of adolescents, fasting serum glucose mean values were -1.3 for placebo (n=95), +0.1 for 40 mg (n=90), and +1.8 for 80 mg (n=32).

Bipolar Depression

Monotherapy
Data from the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study are presented in Table 3.

Table 3: Change in Fasting Glucose in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo 20 to 60 mg/day</th>
<th>LATUDA 20-60 mg/day</th>
<th>LATUDA 80-120 mg/day</th>
<th>LATUDA 120-160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Patients with shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>4.3% (6/141)</td>
<td>2.2% (3/138)</td>
<td>6.4% (9/141)</td>
<td>4.3% (5/118)</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.2 mg/dL at week 24 (n=129).

Adjunctive Therapy with Lithium or Valproate
Data from the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies are presented in Table 4.

Table 4: Change in Fasting Glucose in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Patients with shifts to ≥ 126 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.9</td>
<td>+1.2</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 120 mg/day or placebo as adjunctive therapy with lithium or valproate.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the longer-term study, had a mean change in glucose of +1.7 mg/dL at week 24 (n=88).

Dyslipidemia
Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics.

Schizophrenia

Adults
Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 5.

Table 5: Change in Fasting Lipids in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo 20 mg/day</th>
<th>LATUDA 20-60 mg/day</th>
<th>LATUDA 80-120 mg/day</th>
<th>LATUDA 120-160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Proportion of patients with shifts to ≥ 200 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>5.3% (30/571)</td>
<td>13.8% (8/58)</td>
<td>6.2% (25/402)</td>
<td>5.3% (23/434)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>10.1% (7/749)</td>
<td>10.8% (41/379)</td>
<td>6.3% (25/400)</td>
<td>10.5% (22/209)</td>
</tr>
<tr>
<td>Proportion of patients with shifts to ≥ 240 mg/dL</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>4.0% (4/101)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>7.0% (7/100)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of -3.8 (n=336) and -15.1 (n=357) mg/dL at week 24, -3.1 (n=303) and -4.8 (n=303) mg/dL at week 36 and -2.5 (n=307) and -6.9 (n=307) mg/dL at week 52, respectively.

Adolescents

In the adolescent short-term, placebo-controlled study, fasting serum cholesterol mean values were -9.8 for placebo (n=95), -4.4 for 40 mg (n=89), and +1.6 for 80 mg (n=92), and fasting serum triglyceride mean values were +0.1 for placebo (n=95), -0.6 for 40 mg (n=89), and +8.5 for 80 mg (n=92).

Bipolar Depression

Monotherapy
Data from the adult short-term, flexible-dosed, placebo-controlled, monotherapy bipolar depression study are presented in Table 6.

Table 6: Change in Fasting Lipids in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo 20 to 60 mg/day</th>
<th>LATUDA 20 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>Mean change from baseline (mg/dL)</td>
<td>Mean change from baseline (mg/dL)</td>
</tr>
<tr>
<td>Proportion of patients with shifts to ≥ 200 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol</td>
<td>3.8% (8/571)</td>
<td></td>
</tr>
<tr>
<td>Triglycerides</td>
<td>9.8% (9/100)</td>
<td></td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who received LATUDA as monotherapy in the short-term and continued in the longer-term study had a mean change in total cholesterol and triglycerides of -0.5 (n=130) and -1.0 (n=130) mg/dL at week 24, respectively.
Weight gain has been observed with atypical antipsychotic use. Clinical monitoring of weight is recommended.

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 9. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to +0.2 kg for placebo-treated patients. The proportion of patients with a ≥7% increase in body weight (at Endpoint) was 10.8% for LATUDA-treated patients versus 5.7% for placebo-treated patients.

In the uncontrolled, open-label, longer-term schizophrenia study, patients who received LATUDA as adjunctive therapy with either lithium or valproate in the short-term study and continued in the long-term study, had a mean change in total cholesterol and triglycerides of -0.9 (n=88) and -5.3 (n=88) mg/dL at week 24, respectively.

Weight Gain

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

Schizophrenia

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 9. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to +0.2 kg for placebo-treated patients. Change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.1 ng/mL and was +0.1 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint in prolactin levels was +0.5 ng/mL and for females was +2.6 ng/mL. Median changes for prolactin by dose are shown in Table 12.

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.

Schizophrenia

In short-term, placebo-controlled schizophrenia studies, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +0.4 ng/mL and was -1.9 ng/mL in the placebo-treated patients. The median change from baseline to endpoint for males was +0.5 ng/mL and for females was -0.2 ng/mL. Median changes for prolactin by dose are shown in Table 12.
**Table 13: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Study**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>40 mg/day</th>
<th>80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.10</td>
<td>+0.75</td>
<td>+1.20</td>
</tr>
<tr>
<td>Females</td>
<td>+0.70</td>
<td>+0.60</td>
<td>+4.40</td>
</tr>
<tr>
<td>Males</td>
<td>0.09</td>
<td>+0.75</td>
<td>+1.00</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations >5x ULN was 0.5% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations 5x ULN was 1.3% for LATUDA-treated patients versus 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations 5x ULN was 0% versus 1.6% for placebo-treated male patients.

**Bipolar Depression**

**Adjunctive Therapy with Antipsychotics**

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, was +1.7 ng/mL and +3.5 ng/mL with LATUDA 20 to 60 mg/day and 80 to 120 mg/day, respectively. Compared to 0.3 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +1.5 ng/mL and for females was +1.1 ng/mL. Median changes for prolactin by dose range are shown in Table 14.

**Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 to 60 mg/day</th>
<th>80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>+0.3</td>
<td>+1.7</td>
<td>+3.5</td>
</tr>
<tr>
<td>Females</td>
<td>0.0</td>
<td>+7.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>Males</td>
<td>+0.4</td>
<td>+1.2</td>
<td>+1.9</td>
</tr>
</tbody>
</table>

Patients were randomized to flexibly dosed LATUDA 20 to 60 mg/day, LATUDA 80 to 120 mg/day, or placebo. The proportion of patients with prolactin elevations >5x upper limit of normal (ULN) was 0.4% for LATUDA-treated patients versus 0.0% for placebo-treated patients. 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% versus 0% for placebo-treated male patients.

In the uncontrolled, open-label, longer-term bipolar depression study, patients who were treated with LATUDA, as adjunctive therapy with either lithium or valproate, in the short-term and continued in the longer-term study, had a median change in prolactin of -2.9 ng/mL at week 24 (n=88).

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.

Possible risk factors for leukopenia/neutropenia include pre-existing low white blood cell count (WBC) and history of drug-induced leukopenia/neutropenia. Patients with a pre-existing low 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 decline in WBC, in the absence of other causative factors. Patients with neutropenia should be carefully monitored for fever or other symptoms or signs of infection and treated promptly if such symptoms or signs occur. Patients with severe neutropenia (absolute neutrophil count < 1000/mm^3) should discontinue LATUDA and have their WBC followed until recovery.

Orthostatic Hypotension and Syncope

LATUDA may cause orthostatic hypotension and syncope, perhaps due to its β1-adrenergic receptor antagonism. Associated adverse reactions can include dizziness, lightheadedness, tachycardia, and bradycardia. Generally, these risks are greatest at the beginning of treatment and during dose escalation. Patients at increased risk of these adverse reactions or at increased risk of developing complications from hypotension include those with dehydration, hypovolemia, treatment with antiarrhythmic medication, history of cardiovascular disease (e.g., heart failure, myocardial infarction, ischemia, or conduction abnormalities), history of cerebrovascular disease, as well as patients who are antipsychotic-naïve. In such patients, consider using a lower starting dose and slower titration, and monitor orthostatic vital signs.

Orthostatic hypotension, as assessed by vital sign measurement, was defined by the following vital sign changes: ≥20 mm Hg decrease in systolic blood pressure and ≥10 bpm increase in pulse from sitting to standing or supine to standing position.

Schizophrenia

**Adults**

The incidence of orthostatic hypotension and syncope reported as adverse events from short-term, placebo-controlled schizophrenia studies was (LATUDA incidence, placebo incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0% (0/708)].

In short-term schizophrenia clinical studies, orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.8% with LATUDA 40 mg, 2.1% with LATUDA 80 mg, 1.7% with LATUDA 120 mg and 0.8% with LATUDA 160 mg compared to 0.7% with placebo.

**Adolescents**

The incidence of orthostatic hypotension reported as adverse events from the short-term, placebo-controlled adolescent schizophrenia study was 0.5% (1/212) in LATUDA-treated patients and 0% (0/112) in placebo-treated patients. No syncope event was reported.

Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0% with LATUDA 40 mg and 2.9% with LATUDA 80 mg, compared to 1.8% with placebo.

**Bipolar Depression**

**Orthostatic Hypotension and Syncope**

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 0.6% with LATUDA 20 to 60 mg and 0.0% with LATUDA 40 mg to 120 mg compared to 0% with placebo.

**Adjuvant Therapy with Lithium or Valproate**

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression therapy studies, there were no reported adverse events of orthostatic hypotension and syncope. Orthostatic hypotension, as assessed by vital signs, occurred with a frequency of 1.1% with LATUDA 20 to 120 mg compared to 0.9% with placebo.

**Falls**

LATUDA may cause somnolence, postural hypotension, motor and sensory instability, which may lead to falls and, consequently, fractures or other injuries. For patients with diseases, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating antipsychotic treatment and recurrently for patients on long-term antipsychotic therapy.

**Seizures**

As with other antipsychotic drugs, LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer’s dementia. Conditions that lower the seizure threshold may be more prevalent in patients 65 years or older.

**Schizophrenia**

In adult short-term, placebo-controlled schizophrenia studies, seizures/convulsions occurred in 0.1% (2/1508) of patients treated with LATUDA compared to 0.1% (1/708) placebo-treated patients.
Bipolar Depression

Monotherapy
In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, no patient experienced seizures/convulsions.

Adjuvant Therapy with Lithium or Valproate
In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, no patient experienced seizures/convulsions.

Potential for Cognitive and Motor Impairment
LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills. Caution patients about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

In clinical studies with LATUDA, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Schizophrenia

Adults
In short-term, placebo-controlled schizophrenia studies, somnolence was reported by 17.0% (256/1508) of patients treated with LATUDA (15.5% LATUDA 20 mg, 15.6% LATUDA 40 mg, 15.2% LATUDA 80 mg, 26.5% LATUDA 120 mg and 8.3% LATUDA 160 mg/day) compared to 7.1% (50/708) of placebo patients.

Adolescents
In the short-term, placebo-controlled adolescent schizophrenia study, somnolence was reported by 14.5% (31/214) of patients treated with LATUDA (15.5% LATUDA 40 mg and 13.5% LATUDA 80 mg/day) compared to 7.1% (8/112) of placebo patients.

Bipolar Depression

Monotherapy
In the adult short-term, flexible-dosed, placebo-controlled monotherapy bipolar depression study, somnolence was reported by 7.3% (12/164) and 13.8% (23/167) with LATUDA 20 mg and 80 mg and 120 mg, respectively compared to 6.5% (11/168) of placebo patients.

Adjunctive Therapy with Lithium or Valproate
In the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies, somnolence was reported by 11.4% (41/365) of patients treated with LATUDA 20-120 mg compared to 5.1% (17/334) of placebo patients.

Body Temperature Dysregulation
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.

Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

Dysphagia 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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

Dysphagia 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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

Dysphagia 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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

Activation of Mania/Hypomania
Antidepressant treatment can increase the risk of developing a manic or hypomanic episode, particularly in patients with bipolar disorder. Monitor patients for the emergence of such episodes.

In the bipolar depression monotherapy and adjunctive therapy (with lithium or valproate) studies, less than 1% of subjects in the LATUDA and placebo groups developed manic or hypomanic episodes.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advanced Alzheimer’s dementia.

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 antipsychotics should be used cautiously in elderly patients, in particular those with advance...
Adverse Reactions Associated with Discontinuation of Treatment:

A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Bipolar Depression (Monotherapy)

The following findings are based on the adult short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following findings are based on the short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg (n=331).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were akathisia, extrapyramidal symptoms, somnolence, nausea, vomiting, diarrhea, and anxiety.

Dose-Related Adverse Reactions in the Schizophrenia Studies

Akathisia and extrapyramidal symptoms were dose-related. The frequency of akathisia increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 10.7% for LATUDA 40 mg, 12.3% for LATUDA 60 mg, and 22.0% for LATUDA 120 mg). Akathisia was reported by 7.4% (9/121) of patients receiving 160 mg/day. Akathisia occurred in 3.0% of subjects receiving placebo. The frequency of extrapyramidal symptoms increased with dose up to 120 mg/day (5.6% for LATUDA 20 mg, 11.5% for LATUDA 40 mg, 11.9% for LATUDA 80 mg, and 22.0% for LATUDA 120 mg).

Bipolar Depression (Monotherapy)

The following are the findings based on the adult short-term, placebo-controlled premarketing study for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, nausea, vomiting, diarrhea, and anxiety.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 6.0% (20/331) LATUDA-treated patients and 5.4% (9/168) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence and somnolence.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).

Commonly Observed Adverse Reactions:

The most common adverse reactions (incidence ≥5% and at least twice the rate of placebo) in subjects treated with LATUDA were somnolence andsomnolence.

Adverse Reactions Associated with Discontinuation of Treatment:

A total of 5.8% (21/360) LATUDA-treated patients and 4.8% (16/334) of placebo-treated patients discontinued due to adverse reactions. There were no adverse reactions associated with discontinuation in subjects treated with LATUDA that were at least 2% and at least twice the placebo rate.

Adverse Reactions Occurring at an Incidence of 2% or More in LATUDA-Treated Patients:

The following are the findings based on the adolescent short-term, placebo-controlled premarketing studies for bipolar depression in which LATUDA was administered at daily doses ranging from 20 to 120 mg as adjunctive therapy with lithium or valproate (n=360).
Table 19: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the Adolescent Short-term Schizophrenia Study

<table>
<thead>
<tr>
<th>Body System or Organ Class Dictionary-derived Term</th>
<th>Percentage of Patients Reporting Reaction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (N=112) (%)</td>
</tr>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3</td>
</tr>
<tr>
<td>Vomiting</td>
<td>2</td>
</tr>
<tr>
<td>Dry Mouth</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>0</td>
</tr>
<tr>
<td>Infections and infestations</td>
<td></td>
</tr>
<tr>
<td>Viral infection**</td>
<td>6</td>
</tr>
<tr>
<td>Rhinitis***</td>
<td>2</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>0</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
</tr>
<tr>
<td>Somnolence*</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
</tr>
<tr>
<td>Dizziness</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.
* Viral infection includes adverse event terms: hypoxemia, sedation, and somnolence.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychosis, and tremor.
*** Rhinitis includes adverse event terms: rhinitis, allergic rhinitis, rhinorrhea, and nasal congestion.

Extrapyramidal Symptoms

Schizophrenia

Adults

In the short-term, placebo-controlled schizophrenia studies, for LATUDA-treated patients, the incidence of reported events related to extrapyramidal symptoms (EPS), excluding akathisia and restless lessness, was 13.5% versus 5.8% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 12.9% versus 3.0% for placebo-treated patients. Incidence of EPS by dose is provided in Table 20.

Table 20: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>LATUDA 20 mg/day (N=71) (%)</th>
<th>LATUDA 40 mg/day (N=647) (%)</th>
<th>LATUDA 80 mg/day (N=538) (%)</th>
<th>LATUDA 160 mg/day (N=291) (%)</th>
<th>All LATUDA (N=112) (%)</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>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>13</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>7</td>
</tr>
<tr>
<td>Dystonia</td>
<td>&lt;1</td>
<td>0</td>
<td>4</td>
<td>5</td>
<td>7</td>
<td>2</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>5</td>
<td>6</td>
<td>9</td>
<td>8</td>
<td>17</td>
<td>11</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.
* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychosis, and tremor.

Adolescents

In the short-term, placebo-controlled, study of schizophrenia in adolescents, the incidence of EPS, excluding events related to akathisia, for LATUDA-treated patients was higher in the 40 mg (10%) and the 80 mg (7.7%) treatment groups vs. placebo (3.6%); and the incidence of akathisia-related events for LATUDA-treated patients was 6.9% vs. 1.8% for placebo-treated patients. Incidence of EPS by dose is provided in Table 21.

Table 21: Incidence of EPS Compared to Placebo in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=112) (%)</th>
<th>40 mg/day (N=110) (%)</th>
<th>LATUDA 80 mg/day (N=104) (%)</th>
<th>LATUDA 160 mg/day (N=73) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>14</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>4</td>
<td>7</td>
<td>7</td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.
* Akathisia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychosis, and tremor.

Bipolar Depression

Table 22: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=150) (%)</th>
<th>20 to 60 mg/day (N=164) (%)</th>
<th>LATUDA 80 to 120 mg/day (N=167) (%)</th>
<th>LATUDA 160 mg/day (N=104) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>12</td>
<td>20</td>
<td>9</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Dystonia**</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2</td>
<td>5</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.
* Akathisia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychosis, and tremor.

Adjuvantive Therapy with Lithium or Valproate

Table 23: Incidence of EPS Compared to Placebo in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=334) (%)</th>
<th>LATUDA 20 to 120 mg/day (N=360) (%)</th>
<th>LATUDA 160 mg/day (N=104) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>13</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td>9</td>
<td>24</td>
<td>14</td>
</tr>
<tr>
<td>Akathisia</td>
<td>5</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Dystonia**</td>
<td>&lt;1</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>8</td>
<td>13</td>
<td>13</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer.
* Akathisia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, tardive dyskinesia, and tremor.
** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, glabellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychosis, and tremor.
Schizophrenia

Adulst

The mean change from baseline for LATUDA-treated patients for the SAS, BAS, and AIMS was comparable to placebo-treated patients, with the exception of the Barnes Akathisia Scale global score (LATUDA, 0.1; placebo, 0.0). The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 14.4%; placebo, 7.1%), the SAS (LATUDA, 5.9%; placebo, 2.3%) and the AIMS (LATUDA, 7.4%; placebo, 5.8%).

Adolescents

The mean change from baseline for LATUDA-treated patients with adolescent schizophrenia for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 7.0%; placebo, 1.8%), the SAS (LATUDA, 8.3%; placebo, 2.7%) and the AIMS (LATUDA, 2.8%; placebo, 0.9%).

Bipolar Depression

Monotherapy

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.4%; placebo, 5.6%), the SAS (LATUDA, 3.7%; placebo, 1.9%) and the AIMS (LATUDA, 3.4%; placebo, 1.2%).

Adjunctive Therapy with Lithium or Valproate

The mean change from baseline for LATUDA-treated adult patients for the SAS, BAS and AIMS was comparable to placebo-treated patients. The percentage of patients who shifted from normal to abnormal was greater in LATUDA-treated patients versus placebo for the BAS (LATUDA, 8.7%; placebo, 2.1%), the SAS (LATUDA, 2.8%; placebo, 2.1%) and the AIMS (LATUDA, 2.8%; placebo, 0.6%).

Dystonia

Class Effect: Symptoms of dystonia, prolonged abnormal contractions of muscle groups, may occur in susceptible individuals during the first few days of treatment. Dystonic symptoms include: spasm of the neck muscles sometimes progressing to tightness of the throat, swallowing difficulty, difficulty breathing, and/or protrusion of the tongue. While these symptoms can occur at low doses, they occur more frequently and with greater severity with high potency and at higher doses of first-generation antipsychotic drugs. An elevated risk of acute dystonia is observed in males and younger age groups.

Schizophrenia

Adults

In the short-term, placebo-controlled schizophrenia clinical studies, dystonia occurred in 4.2% of LATUDA-treated subjects (0.0% LATUDA 20 mg, 3.5% LATUDA 40 mg, 4.5% LATUDA 80 mg, 6.5% LATUDA 120 mg and 2.5% LATUDA 160 mg) compared to 0.8% of subjects receiving placebo. Seven subjects (0.5% 7/1508) discontinued clinical trials due to dystonic events – four were receiving LATUDA 80 mg/day and three were receiving LATUDA 120 mg/day.

Adolescents

In the short-term, placebo-controlled, adolescent schizophrenia study, dystonia occurred in 1% of LATUDA-treated patients (1% LATUDA 40 mg and 1% LATUDA 80 mg) compared to 0% of patients receiving placebo. No patients discontinued the clinical study due to dystonic events.

Bipolar Depression

Monotherapy

In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, dystonia occurred in 0.9% of LATUDA-treated subjects (0.0% and 1.8% for LATUDA 20 to 60 mg/day and LATUDA 80 to 120 mg/day, respectively) compared to 0.0% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Adjunctive Therapy with Lithium or Valproate

In the adult short-term, flexible-dose, placebo-controlled adjunctive therapy bipolar depression studies, dystonia occurred in 1.1% of LATUDA-treated subjects (20 to 120 mg) compared to 0.6% of subjects receiving placebo. No subject discontinued the clinical study due to dystonic events.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA

Following is a list of adverse reactions reported by adult patients treated with LATUDA at multiple doses of ≥20 mg once daily within the premarketing database of 2905 patients with schizophrenia. The reactions listed are those that could be of clinical importance, as well as reactions that are plausibly drug-related on pharmacologic or other grounds. Reactions listed in Table 18 or those that appear elsewhere in the LATUDA label are not included. Although the reactions reported occurred during treatment with LATUDA, they were not necessarily caused by it.

Reactions are further categorized by organ class and listed in order of decreasing frequency according to the following definitions: those occurring in at least 1/100 patients (frequent) (only those not already listed in the tabulated results from placebo-controlled studies appear in this listing); those occurring in 1/100 to 1/1000 patients (infrequent); and those occurring in fewer than 1/1000 patients (rare).

Blood and Lymphatic System Disorders: Infrequent: anemia

Cardiac Disorders: Frequent: tachycardia, Infrequent: AV block 1st degree, angina pectoris, Bradycardia

Ear and Labyrinth Disorders: Infrequent: vertigo

Eye Disorders: Frequent: blurred vision

Gastrointestinal Disorders: Frequent: abdominal pain, diarrhea; Infrequent: gastritis

General Disorders and Administrative Site Conditions: Rare: sudden death

Investigations: Frequent: CPK increased

Metabolism and Nutritional System Disorders: Frequent: decreased appetite

Musculoskeletal and Connective Tissue Disorders: Rare: rhabdomyolysis

Nervous System Disorders: Infrequent: cerebrovascular accident, dystarhria

Psychiatric Disorders: Infrequent: abnormal dreams, panic attack, sleep disorder

Renal and Urinary Disorders: Infrequent: dysuria; Rare: renal failure

Reproductive System and Breast Disorders: Infrequent: amenorrhea, dysmenorrhea; Rare: breast enlargement, breast pain, galactorrhea, erectile dysfunction

Skin and Subcutaneous Tissue Disorders: Frequent: rash, pruritus; Rare: angioedema

Vascular Disorders: Frequent: hypertension

Clinical Laboratory Change

Schizophrenia

Serum Creatinine: In short-term, placebo-controlled trials, the mean change from Baseline in serum creatinine was +0.05 mg/dL for LATUDA-treated patients compared to +0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 3.0% (43/1453) of LATUDA-treated patients and 1.6% (11/681) on placebo. The threshold for high creatinine value varied from >0.79 to >1.3 mg/dL based on the centralized laboratory definition for each study (Table 24).

Table 24: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laboratory</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
<th>LATUDA 120 mg/day</th>
<th>LATUDA 160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>(N=71)</td>
<td>(N=291)</td>
<td>(N=121)</td>
<td>(N=103)</td>
<td>(N=97)</td>
<td>(N=291)</td>
<td>(N=167)</td>
</tr>
<tr>
<td>%</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>7%</td>
<td>2%</td>
</tr>
</tbody>
</table>

Adolescents

Serum Creatinine: In the short-term, placebo-controlled, adolescent schizophrenia study, the mean change from Baseline in serum creatinine was −0.009 mg/dL for LATUDA-treated patients compared to +0.017 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 7.2% (14/194) of LATUDA-treated patients and 2.9% (3/103) on placebo (Table 25).

Table 25: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laboratory</th>
<th>Placebo</th>
<th>LATUDA 20 mg/day</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 80 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>(N=103)</td>
<td>(N=167)</td>
<td>(N=164)</td>
<td>(N=167)</td>
<td>(N=167)</td>
</tr>
<tr>
<td>%</td>
<td>2.9%</td>
<td>7.2%</td>
<td>7.2%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Bipolar Depression

Monotherapy

Serum Creatinine: In the adult short-term, flexible-dose, placebo-controlled monotherapy bipolar depression study, the mean change from Baseline in serum creatinine was +0.01 mg/dL for LATUDA-treated patients compared to −0.02 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 2.8% (9/322) of LATUDA-treated patients and 0.6% (1/168) on placebo (Table 26).

Table 26: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Laboratory</th>
<th>Placebo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>(N=168)</td>
<td>(N=164)</td>
<td>(N=167)</td>
<td>(N=167)</td>
</tr>
<tr>
<td>%</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
<td>2%</td>
</tr>
</tbody>
</table>
Adjuvant Therapy with Lithium or Valproate
Serum Creatinine: In adult short-term, placebo-controlled premarketing adjuvant studies for bipolar depression, the mean change from Baseline in serum creatinine was +0.04 mg/dL for LATUDA-treated patients compared to -0.01 mg/dL for placebo-treated patients. A creatinine shift from normal to high occurred in 4.3% (15/360) of LATUDA-treated patients and 1.6% (5/334) on placebo (Table 27).

Table 27: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjuvant Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=334)</th>
<th>LATUDA 20 to 120 mg/day (N=360)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Postmarketing Experience
The following adverse reactions have been identified during postapproval use of Latuda. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity Reactions: Urticaria, throat swelling, tongue swelling, and dyspnea.

DRUG INTERACTIONS

Drugs Having Clinically Important Interactions with LATUDA

Table 28: Clinically Important Drug Interactions with Latuda

<table>
<thead>
<tr>
<th>DRUG INTERACTIONS</th>
<th>Clinical Impact</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitors</td>
<td>Concomitant use of LATUDA with strong CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone.</td>
<td>Ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil</td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>LATUDA dose should be reduced to half of the original level when used concomitantly with moderate inhibitors of CYP3A4.</td>
<td>Diltiazem, atazanavir, erythromycin, fluconazole, verapamil</td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone.</td>
<td>Rifampin, avasimibe, St. John's wort, phenytoin, carbamazepine</td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Concomitant use of LATUDA with moderate CYP3A4 inhibitors increased the exposure of lurasidone compared to the use of LATUDA alone.</td>
<td>Ketoconazole, clarithromycin, ritonavir, voriconazole, mibefradil</td>
</tr>
<tr>
<td>Clinical Impact</td>
<td>Concomitant use of LATUDA with strong CYP3A4 inducers decreased the exposure of lurasidone compared to the use of LATUDA alone.</td>
<td>Diltiazem, atazanavir, erythromycin, fluconazole, verapamil</td>
</tr>
</tbody>
</table>

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK Field Change and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Strong CYP3A4 Inhibitor</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Ketoconazole</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Moderate CYP3A4 Inhibitor</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Verapamil</td>
<td>240 mg/day</td>
</tr>
<tr>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Strong CYP3A4 Inducer</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Rifampin</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Cmax</td>
<td>AUC</td>
</tr>
<tr>
<td>Lithium</td>
<td>600 mg BID</td>
</tr>
<tr>
<td>Cmax</td>
<td>AUC</td>
</tr>
</tbody>
</table>

Drugs Having No Clinically Important Interactions with LATUDA

Based on pharmacokinetic studies, no dosage adjustment of LATUDA is required when administered concurrently with lithium, valproate, or substrates of P-gp or CYP3A4.

Figure 2: Impact of LATUDA on Other Drugs

<table>
<thead>
<tr>
<th>Interacting drug</th>
<th>PK Field Change and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>P-gp Substrates</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Erythromycin</td>
<td>0.25 mg BID</td>
</tr>
<tr>
<td>CYP3A4 Substrates</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Midazolam</td>
<td>5 mg BID</td>
</tr>
<tr>
<td>Oral Contraceptives</td>
<td>Cmax AUC</td>
</tr>
<tr>
<td>Ethinyl Estradiol</td>
<td>1 mg day</td>
</tr>
<tr>
<td>Norethisterone</td>
<td>4 mg day</td>
</tr>
<tr>
<td>Lithium</td>
<td>600 mg BID*</td>
</tr>
</tbody>
</table>

USE IN SPECIFIC POPULATIONS

Pregnancy

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to LATUDA during pregnancy. For more information, contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit https://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry.

Risk Summary

Neonates exposed to antipsychotic drugs during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There are no studies of LATUDA use in pregnant women. The limited available data are not sufficient to inform a drug-associated risk of birth defects or miscarriage. In animal reproduction studies, no teratogenic effects were seen in pregnant rats and rabbits given lurasidone during the period of organogenesis at doses approximately 1.5- and 6-times, the maximum recommended human dose (MRHD) of 160 mg/day, respectively based on mg/m² body surface area.

The estimated background risk of major birth defects and miscarriage for the indicated population(s) is unknown. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hyperactivity, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates who were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Pregnant rats were treated with oral lurasidone at doses of 3, 10, and 25 mg/kg/day during the period of organogenesis. These doses are 0.2, 0.6, and 1.5 times the MRHD of 160 mg/day based on mg/m² body surface area. No teratogenic or embryo-fetal effects were observed up to 1.5 times the MRHD of 160 mg/day, based on mg/m².

Pregnant rabbits were treated with oral lurasidone at doses of 0.4, 2, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m². No teratogenic or embryo-fetal effects were observed up to 6 times the MRHD of 160 mg/kg based on mg/m².

Pregnant rats were treated with oral lurasidone at doses of 2, 10, and 50 mg/kg/day during the period of organogenesis. These doses are 0.2, 1.2 and 6 times the MRHD of 160 mg/day based on mg/m². No teratogenic or embryo-fetal effects were observed up to 6 times the MRHD of 160 mg/kg based on mg/m².

Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of lurasidone in human milk, the effects on the breastfed infant, or the effects on milk production. Lurasidone is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother’s clinical need for LATUDA and any potential adverse effects on the breastfed infant from LATUDA or from the underlying maternal condition.

Supplement to Current Psychiatry S13
Pediatric Use

Schizophrenia

The safety and effectiveness of LATUDA 40-mg/day and 80-mg/day for the treatment of schizophrenia in adolescents (13 to 17 years) was established in a 6-week, placebo-controlled clinical study in 326 adolescent patients.

Depression

The safety and effectiveness of LATUDA have not been established in pediatric patients with depression.

Irritability-Associated with Autistic Disorder

The effectiveness of LATUDA in pediatric patients for the treatment of irritability associated with autistic disorder has not been established.

Efficacy was not demonstrated in a 6-week study evaluating LATUDA 20 mg/day and 60 mg/day for the treatment of pediatric patients 6 to 17 years of age with irritability associated with autistic disorder diagnosed by Diagnostic and Statistical Manual of Mental Disorders, 4th Ed., Text Revision (DSM-IV-TR) criteria. The primary objective of the study as measured by improvement from Baseline in the irritability subscale of the Aberrant Behavior Checklist (ABC) at Endpoint (Week 6) was not met. A total of 149 patients were randomized to LATUDA or placebo. Vomiting occurred at a higher rate than reported in other LATUDA studies (4/49 or 8% for 20 mg, 14/51 or 27% for 60 mg, and 2/49 or 4% for placebo), particularly in children aged 6 to 12 (13 out of 18 patients on LATUDA with vomiting).

Juvenile animal studies

Adverse effects were seen on growth, physical and neurobehavioral development at doses as low as 0.2 times the MRHD based on mg/m². Lurasidone was orally administered to rats from postnatal days 21 through 91 (this period corresponds to childhood, adolescence, and young adulthood in humans) at doses of 3, 30, and 150 (males) or 300 (females) mg/kg/day which are 0.2 to 10 times (males) and 20 times (females) the maximum recommended adult human dose (MRHD) of 160 mg/day based on mg/m². The adverse effects included dose-dependent decreases in femoral length, bone mineral content, body and brain weights at 2 times the MRHD in both sexes, and motor hyperactivity at 0.2 and 2 times the MRHD in both sexes based on mg/m². In females, there was a delay in attainment of sexual maturity at 2 times the MRHD, associated with decreased estrus estradiol. Mortality occurred in both sexes during early post-weaning period and some of the male weanlings died after only 4 treatments at doses as low as 2 times the MRHD based on mg/m². Histopathological findings included increased colloid in the thyroids and inflammation of the prostate in males at 10 times MRHD based on mg/m². Some of these findings were attributed to transiently elevated serum prolactin which was seen in both sexes at all doses. However, there were no changes at any dose level in reproductive parameters (fertility, conception indices, spermatogenesis, estrous cycle, gestation length, parturition, number of pups born). The no effect dose for neurobehavioral changes in males is 0.2 times the MRHD based on mg/m² and could not be determined in females. The no effect dose for growth and physical development in both sexes is 0.2 times the MRHD based on mg/m².

Geriatric Use

Clinical studies with LATUDA did not include sufficient numbers of patients aged 65 and older to determine whether or not they respond differently from younger patients. In elderly patients with psychosis (65 to 85), LATUDA concentrations (20 mg/day) were similar to those in young subjects. It is unknown whether dose adjustment is necessary on the basis of age alone.

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

Renal Impairment

Reduce the maximum recommended dosage in patients with moderate or severe renal impairment (Clcr<50 mL/minute). Patients with impaired renal function (Clcr<50 mL/minute) had higher exposure to lurasidone than patients with normal renal function. Greater exposure may increase the risk of LATUDA-associated adverse reactions.

Hepatic Impairment

Reduce the maximum recommended dosage in patients with moderate to severe hepatic impairment (Child-Pugh score >7). Patients with moderate to severe hepatic impairment (Child-Pugh score >7) generally had higher exposure to lurasidone than patients with normal hepatic function. Greater exposure may increase the risk of LATUDA-associated adverse reactions.

Other Specific Populations

No dosage adjustment for LATUDA is required on the basis of a patient’s sex, race, or smoking status.

Studies in Specific Populations

The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.

Pediatric Patients

LATUDA exposure (i.e., steady-state Cmax and AUC) in children and adolescent patients (10 to 17 years of age) was generally similar to that in adults across the dose range from 40 to 160 mg, without adjusting for body weight.

Figure 3: Impact of Other Patient Factors on LATUDA Pharmacokinetics

<table>
<thead>
<tr>
<th>PK</th>
<th>Change Relative to Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>1.0</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.1</td>
</tr>
<tr>
<td>Severe</td>
<td>1.2</td>
</tr>
</tbody>
</table>

*Compared to Control

DRUG ABUSE AND DEPENDENCE

Controlled Substance

LATUDA is not a controlled substance.

Abuse

LATUDA has not been systematically studied in humans for its potential for abuse or physical dependence or its ability to induce tolerance. While clinical studies with LATUDA did not reveal any tendency for drug-seeking behavior, these observations were not systematic and it is not possible to predict the extent to which a CNS-active drug will be misused, diverted and/or abused once it is marketed. Patients should be evaluated carefully for a history of drug abuse, and such patients should be observed carefully for signs of LATUDA misuse or abuse (e.g., development of tolerance, drug-seeking behavior, increases in dose).

OVER DOSAGE

Human Experience

In premarketing clinical studies, accidental or intentional overdosage of LATUDA was identified in one patient who ingested an estimated 560 mg of LATUDA. This patient recovered without sequelae. This patient resumed LATUDA treatment for an additional two months.

Management of Overdosage

No specific antidotes for LATUDA are known. In managing overdose, provide supportive care, including close medical supervision and monitoring, and consider the possibility of multiple drug involvement. If an overdose occurs, consult a Certified Poison Control Center (1-800-222-1222 or www.poison.org). Cardiovascular monitoring should commence immediately, including continuous electrocardiographic monitoring for possible arrhythmias. If antiarrhythmic therapy is administered, disopyramide, procainamide, and quinidine carry a theoretical hazard of additive QT-prolonging effects when administered in patients with an acute overdose of LATUDA. Similarly, the alpha-blocking properties of bretylium might be additive to those of LATUDA, resulting in problematic hypotension.

Hypotension and circulatory collapse should be treated with appropriate measures. Epinephrine and dopamine should not be used, or other sympathomimetics with beta-agonist activity, since beta stimulation may worsen hypotension in the setting of LATUDA-induced alpha blockade. In case of severe extrapyramidal symptoms, anticholinergic medication should be administered. Gastric lavage (after intubation if patient is unconscious) and administration of activated charcoal together with a laxative should be considered. The possibility of obtundation, seizures, or dystonic reaction of the head and neck following overdose may create a risk of aspiration with induced emesis.