The Eating Disorders Work Group of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition Task Force was given the charge of considering whether obesity is a mental disorder that should be included.

There were several reasons for considering the salience of obesity for the psychiatric nomenclature. First, phenotypic similarities in the behaviors associated with obesity and both eating disorders and substance use disorders, as well as findings documenting different brain responses to food-related cues in lean and obese individuals, have led to consideration of obesity as a mental disorder.

Next, there is growing evidence documenting a relation between obesity and numerous psychiatric disorders. Finally, increasing concern about the association of psychotropic drugs with weight gain and increases in cardiometabolic risk has led to enhanced awareness of obesity in psychiatry. Nevertheless, there currently is insufficient evidence to include obesity in DSM-5. In the sections that follow, we outline research findings that informed the decision making of the Eating Disorders Work Group.

CHARACTERISTICS OF OBESITY

Obesity refers to an excess of body fat. In the broadest sense, obesity is
caused by a long-term imbalance between energy intake and energy expenditure resulting in the storage of non-essential lipids in adipose cells. There is no clear demarcation between normal and abnormal levels of body fat, and obesity is most commonly estimated by various proxies. Currently, body mass index (BMI), which is a ratio of weight to height that is calculated by weight in kilograms divided by height in meters squared, is used most commonly to define obesity operationally. BMI is strongly associated with adiposity and obesity-related morbidity, and category thresholds have been established (BMI < 18.5 – underweight; BMI 18.5-24.9 – normal weight; BMI 25-29.9 – overweight; BMI > 30 – obese).  

Since the middle of the 20th century, rates of obesity in the United States have increased dramatically in men and women, and in all racial/ethnic and socioeconomic groups. There is some evidence that the striking increases in obesity have leveled off; nevertheless, the prevalence of obesity in the US in 2009-2010 was 35.5% in adult men and 35.8% among adult women, and there is no indication that prevalence is decreasing.  

Obesity has profound medical consequences and is associated with cardiovascular disease, hypertension, type 2 diabetes, and certain types of cancer. Obesity also is related to psychosocial impairments and poorer quality of life. Health care costs associated with obesity were estimated to account for 9.1% of US medical expenses in 1998, and if current trends continue, obesity will account for 16% of US health care expenditures by 2030.  

The substantial personal and societal burden incurred by obesity has led The Obesity Society to declare on utilitarian grounds that obesity is a disease in order to promote research, reduce stigma, and facilitate professional care. Indeed, in light of the medical morbidity and costs associated with obesity, research focusing on the causes, consequences, and treatment of obesity is a public health priority.

**ETIOLOGY OF OBESITY**  
The causes of obesity are incompletely understood. At a population level, many epidemiologists have concluded that the increased prevalence of obesity may be due primarily to modest increases in calorie intake and decreases in physical activity that have led to overall upward shifts in population weights. At an individual level, however, there is agreement that causes are heterogeneous and involve an intricate interplay among genetic, individual, environmental, and societal factors. Research in obesity has increased exponentially with work across multiple levels of analysis from the molecular to the macroeconomic.  

Findings suggest that obesity results from varying alterations of complex internal and environmental milieus that interact to result in a diversity of phenotypes. In light of the multiple pathways to obesity, the DSM-5 Eating Disorders Work Group concluded that there is little evidence to support the conclusion that obesity per se is a mental disorder. Nevertheless, it certainly is possible that particular obesity phenotypes are the consequence of mental disorder.

**BEHAVIORAL PHENOTYPES OF OBESITY**  
**Obesity and Binge Eating**  

In a paper examining the potential role for obesity-related diagnoses in the DSM-5, Devlin proposed eating disorders (EDs), in particular binge eating disorder (BED), or substance use disorders (SUDs) as two models for including obese phenotypes characterized by “non-normative obesity-promoting overeating.” BED, which has been recommended for inclusion in the DSM-5 as an ED, is characterized by persistent and frequent ingestion of large amounts of food coupled with a loss of control over the aberrant eating, which are associated with clinically significant distress and dysfunction.  

Available evidence has indicated that recurrent binge eating is associated with weight gain. Moreover, there is a strong relationship between BED and obesity in clinical and community samples, as well as an association between severity of binge eating and degree of overweight. Thus, there already is a diagnosis in the DSM for an obesity phenotype characterized by aberrant eating. Nevertheless, it is important to recognize that not all individuals with BED are obese, and conversely, the vast majority of obese individuals do not have BED. Thus, inclusion of BED in the DSM-5 will not address the question of obesity as a psychiatric disorder completely.

**Obesity as an SUD**  

An alternate conceptualization would be to classify obesity as an SUD based on phenotypic similarities between drug-seeking in individuals who are addicted to drugs and food-seeking in obese individuals, who ostensibly are addicted to food. In an addiction model of obesity, certain foods, in particular those that are highly palatable, are theorized to co-opt central reward neurocircuitry in a manner analogous to that seen in other SUDs. Observers have noted evidence of compulsive food-seeking and the development of tolerance, withdrawal, and loss of control over eating in obese individuals, with persistence of overeating despite adverse consequences for the individual.  

However, considering obesity as an SUD is problematic for several reasons, including that food, unlike drugs of abuse, is necessary for survival, and there is no compelling evidence of human withdrawal symptoms from foods. In addition, not all obese individuals
report patterns of behavior consistent with food addiction or substance abuse.

A more nuanced stance might be to consider whether the concept of food addiction is most salient for individuals with clearly aberrant eating, ie, those with BED. Nevertheless, not all individuals with BED are phenotypically similar to those with SUD, and there are compelling arguments that models utilizing clinical phenomenology of EDs or SUDs to conceptualize psychiatric phenotypes of obesity are too imprecise to evaluate critically.

Advances in understanding are likely to emerge from work examining the neurobiology of obese phenotypes across these psychiatric disorders. For example, there has been an explosion of work in neuroscience, particularly from studies utilizing functional neuroimaging, which has focused on the potential dysfunction of central pathways that may be involved in obesity-related eating behavior.

The notion that obesity may be understood in the context of the neurobiological framework of addiction, if not as a SUD per se, has gained increasing attention. In particular, Volkow and colleagues, informed by work in animal and human models of addiction, have posited that in vulnerable people (by virtue of genetic liability or other individual factors), reinforcers in the form of food or drugs become overvalued relative to other reinforcers as a result of conditioned learning.

Then, an elevated expected or anticipated reward from food or drugs overactivates memory and reward circuits and inhibits cognitive control circuitry, which in turn, leads to an inability to self-manage the drive to consume drugs or foods.

Support for various components of the model come from burgeoning evidence documenting differences between obese and lean individuals in neural responding in pathways that involve reward sensitivity, conditioned learning and cognitive control, as well as data that elucidate how hypothalamic neuropeptides that regulate energy balance affect the activity of dopamine cells in reward pathways.

Nevertheless, numerous questions remain. There is little evidence that differences in neural activation in response to food-related or non–food-related re-

The exact causes for the comorbidity of obesity and non-eating or substance-related mental disorders remain unknown.

COMORBID PSYCHIATRIC DISORDERS AND OBESITY

The relation between obesity and psychiatric disorder is not limited to EDs and SUDs. A growing body of evidence from epidemiologic and community samples has documented a relationship between obesity and other psychiatric disorders, including mood and anxiety disorders, as well as personality disorder. Moreover, developing evidence has suggested a relationship between obesity and attention-deficit/hyperactivity disorder (ADHD) and posttraumatic stress disorder.

The exact causes for the comorbidity of obesity and non-eating or substance-related mental disorders remain unknown. However, there are several possible explanations. For example, obesity shares a number of symptom atic features in common with mood disorders, including increased appetite, decreased activity levels, and sleep disturbance. Indeed, changes in weight status or eating behavior are included in the current DSM criteria for major depressive episodes, dysthymia, and borderline personality disorder.

Obesity also shares a number of correlates in common with mental disorders in addition to those noted with regard to EDs and SUDs, including hypothalamic-pituitary-adrenal (HPA) axis dysregulation and environmental precipitants such as childhood trauma. Thus, it is possible that increased adiposity in psychiatric patients may signal the presence of clinically relevant third variables that might have relevance for course or outcome.

The ubiquity of the relationships between obesity and numerous psychiatric disorders highlights both the heterogeneity of obesity and the limitations inherent in descriptive diagnostic categories.

The current understanding of mental disorder encompasses multiple levels of analysis, including genetics, brain circuitry, and behavioral factors, and does not always correspond clearly to the current symptom-based psychiatric nosology. This has led to increased interest in efforts to examine conceptually relevant dimensions associated with psychiatric disorder that will guide investigations designed to identify meaningful distinctions and similarities across the range of psychiatric diagnoses. This approach is exemplified by the National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) project.

Thus, a more complete understanding of the relationships among eating pathology, obesity and the range of
psychiatric disorders is likely to involve examination of these phenomena across psychiatric classes to identify neurobiological factors that underlie phenotypic similarities (eg, binge eating in mood disorder, BED, and borderline personality disorder) and distinguish lean from obese individuals. As there is complexity and redundancy of central and peripheral mechanisms involved in the regulation of energy, this will require additional studies focusing on the neurobiology of reward, but also broadening the investigative focus to examine patterns of responding in other disorders where obesity and aberrant eating are common.

Such studies will need to include other relevant domains of neural responding such as those involved in threat or arousal systems that govern sleep. In addition, these data will need to be integrated with findings that explicate the homeostatic systems involved with energy regulation (ie, hunger and satiety) and their interaction with central systems implicated in psychiatric disorder.

Overall, the research designed to elucidate the role and function of central mechanisms associated with psychiatric and obese phenotypes shows great promise for promoting understanding of the relationship between obesity and psychiatric dysfunction. However, the complex and heterogeneous nature of this relationship highlights the problems of including obesity as a distinct disorder in DSM-5.

PSYCHOTROPIC DRUGS AND OBESITY

An additional factor that has prompted interest in the salience of obesity to psychiatry is the effect of psychotropic drugs on body weight. Many psychiatric medications available currently are associated with weight gain, but there has been a particular focus on the potential iatrogenic effects of second-generation antipsychotic agents, especially clozapine and olanzapine. Medication-induced weight gain has been linked to noncompliance with treatment and the development of obesity and its related comorbidities. However, because psychiatric medications affect multiple and diverse aspects of central functioning, there is no single cause of psychotropic-associated weight gain. There also is marked variation in medication-induced weight gain across patients.

Future research may help to identify patients at highest risk for significant weight gain and metabolic risk. For example, a recent study documented that a locus near the melanocortin 4 receptor gene was associated with extreme weight gain from second-generation antipsychotic medications.

In light of the potential effects of psychiatric medications on the development of obesity and associated medical comorbidities, it is critical that clinicians select medications carefully and monitor side effects closely. Moreover, it is advisable to include BMI as an index of adiposity in the assessment and management of all psychiatric illnesses. Referral for additional medical assessment is recommended for individuals with marked increases in weight during treatment.

CONCLUSION

In summary, the Eating Disorders Work Group concluded that obesity should not be included in DSM-5. Obesity is a heterogeneous condition with a complex and incompletely understood etiology, and thus cannot be considered a mental disorder per se. There may be obesity phenotypes that are caused by mental disorder, but research focusing on the role of neural mechanisms in the onset and maintenance of obesity and obesity-related behaviors (eg, overeating) is in its infancy.

Future work focusing on conceptually relevant biological dimensions that may underlie both obesity and psychiatric disorders could shed light on the role of mental dysfunction in the expression of psychiatrically relevant obesity subtypes. Nevertheless, obesity is associated with numerous psychiatric disorders, and several classes of psychotropic medications are associated with weight gain, metabolic risk factors, and obesity. Consequently, clinicians are advised to monitor weight and BMI closely and to consider the salience of overeating and weight-related issues in patients with psychiatric disorders.

REFERENCES


AD INDEX

SLACK INCORPORATED
6900 Grove Rd, Thorofare, NJ 08086
Healio.com/Psychiatry.................... 397

SUNOVION PHARMACEUTICALS INC.
84 Waterford Dr.
Marlborough, MA 01752
Latuda........................................436-440,C3,C4

While every precaution is taken to ensure accuracy, we cannot guarantee against occasional changes or omissions in the preparation of this index.
INDICATIONS AND USAGE
LATUDA is an atypical antipsychotic agent indicated for the treatment of patients with schizophrenia. Efficacy was established in five 6-week controlled studies of adult patients with schizophrenia. The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

IMPORTANT SAFETY INFORMATION FOR LATUDA

WARNING: INCREASED MORTALITY IN ELDERLY PATIENTS WITH DEMENTIA-RELATED PSYCHOSIS
See full prescribing information for complete boxed warning.
• Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death.
• LATUDA is not approved for the treatment of patients with dementia-related psychosis.

CONTRAINDICATIONS
LATUDA is contraindicated in the following:
• Any patient with a known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone.
• Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole).
• Concomitant use with strong CYP3A4 inducers (e.g., rifampin).

WARNINGS AND PRECAUTIONS
Cerebrovascular Adverse Reactions, Including Stroke: LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS, a potentially fatal symptom complex, has been reported with administration of antipsychotic drugs, including LATUDA. NMS can cause hyperpyrexia, muscle rigidity, altered mental status and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. 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.

Tardive Dyskinesia (TD): The risk of developing TD and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. Given these considerations, LATUDA should be prescribed in a manner that is most likely to minimize the occurrence of TD. If signs and symptoms appear in a patient on LATUDA, drug discontinuation should be considered.

Metabolic Changes
Hyperglycemia and Diabetes Mellitus: Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

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

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

Hyperprolactinemia: As with other drugs that antagonize dopamine D2 receptors, LATUDA elevates prolactin levels. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported in patients receiving prolactin-elevating compounds.

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported during treatment with antipsychotic agents. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Patients with a preexisting low white blood cell count (WBC) or a history of drug induced leukopenia/neutropenia should have their complete blood count (CBC) monitored frequently during the first few months of therapy, and LATUDA should be discontinued at the first sign of a decline in WBC in the absence of other causative factors.

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

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

Potential for Cognitive and Motor Impairment: In short-term, placebo-controlled trials, somnolence was reported in 17.0% (50/708) of placebo patients, respectively. Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Suicide: The possibility of suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

ADVERSE REACTIONS
Commonly Observed Adverse Reactions: (incidence ≥5% and at least twice the rate of placebo) in patients treated with LATUDA were somnolence, akathisia, nausea and parkinsonism.

Please see brief summary of prescribing information on adjacent pages, including Boxed Warning.


FOR MORE INFORMATION, PLEASE CALL 1-888-394-7377 OR VISIT www.LatudaHCP.com.
WARNING: 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 [see Warnings and Precautions (5.1)].
- LATUDA is not approved for use in patients with dementia-related psychosis [see Warnings and Precautions (5.1)].

1 INDICATIONS AND USAGE

LATUDA is indicated for the treatment of patients with schizophrenia.

The efficacy of LATUDA in schizophrenia was established in five 6-week controlled studies of adult patients with schizophrenia [Clinical Studies (14.1)].

The effectiveness of LATUDA for longer-term use, that is, for more than 6 weeks, has not been established in controlled studies. Therefore, the physician who elects to use LATUDA for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient [see Dosage and Administration (2)].

4 CONTRAINDICATIONS

LATUDA is contraindicated in the following:

- Any patient with a known hypersensitivity to lurasidone HCI or any components in the formulation. Angioedema has been observed with lurasidone [see Adverse Reactions (6.1)].
- Concomitant use with strong CYP3A4 inhibitors (e.g., ketoconazole) [see Drug Interactions (7.1)].
- Concomitant use with strong CYP3A4 inducers (e.g., rifampin) [see Drug Interactions (7.1)].

5 WARNINGS AND PRECAUTIONS

5.1 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) of antipsychotic drugs in patients with dementia-related psychosis revealed a risk of death in drug-treated patients of between 1.6- to 1.7-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 patients is not clear. LATUDA is not approved for the treatment of patients with dementia-related psychosis [see Boxed Warning].

5.2 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 [see also Boxed Warning and Warnings and Precautions (5.1)].

5.3 Neuroleptic Malignant Syndrome

A potentially fatal syndrome 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 dysrhythmia). Additional signs may include elevated temperature, hypoglycemia, 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, septicemia) 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.

5.4 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 on 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 cumulative 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 upon 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.

5.5 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 extreme and associated with ketoacidosis 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.

Pooled data from short-term, placebo-controlled studies are presented in Table 1.

Table 1: Change in Fasting Glucose

<table>
<thead>
<tr>
<th>LATUDA</th>
<th>Placebo</th>
<th>20 mg/day</th>
<th>40 mg/day</th>
<th>60 mg/day</th>
<th>80 mg/day</th>
<th>120 mg/day</th>
<th>160 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=680</td>
<td>n=71</td>
<td>n=478</td>
<td>n=508</td>
<td>n=283</td>
<td>n=113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.0</td>
<td>-0.6</td>
<td>2.6</td>
<td>-0.4</td>
<td>2.5</td>
<td>2.5</td>
<td></td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts ≥ 126 mg/dL

<table>
<thead>
<tr>
<th>Serum Glucose (≥126 mg/dL)</th>
<th>8.3%</th>
<th>11.7%</th>
<th>12.7%</th>
<th>6.8%</th>
<th>10.0%</th>
<th>5.6%</th>
</tr>
</thead>
</table>

In the uncontrolled, long-term 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).

Dyslipidemia

Undesirable alterations in lipids have been observed in patients treated with atypical antipsychotics. Pooled data from short-term, placebo-controlled studies are presented in Table 2.
As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin, which may lead to decreased bone density in both female and male patients. Amenorrhea, gynecomastia, and impotence have been reported with prolactin-imparing gonadal steroidogenesis in both female and male patients. Galactorrhea, breast cancer. As is common with compounds which increase prolactin release, an increased risk of breast cancer in women is a concern.

Table 2: Change in Fasting Lipids

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
<tr>
<td>n=660</td>
<td>n=71</td>
</tr>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td></td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>–5.8</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>–13.4</td>
</tr>
</tbody>
</table>

Table 3: Mean Change in Weight (kg) from Baseline

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=696)</td>
<td>(n=71)</td>
</tr>
<tr>
<td>20 mg/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>–0.02</td>
<td>–0.15</td>
</tr>
</tbody>
</table>

In the uncontrolled, long-term studies (primarily open-label extension studies), LATUDA was associated with a mean change in total cholesterol and triglycerides of –3.8 (n=356) 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.

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

Disruption of the body’s ability to reduce core body temperature has been attributed to LATUDA. In short-term, placebo-controlled studies, the mean 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 mean 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 5.

Table 4: Median Change in Prolactin (ng/mL) from Baseline

<table>
<thead>
<tr>
<th>Placebo</th>
<th>LATUDA</th>
</tr>
</thead>
<tbody>
<tr>
<td>(n=596)</td>
<td>(n=71)</td>
</tr>
<tr>
<td>20 mg/day</td>
<td>40 mg/day</td>
</tr>
<tr>
<td>–1.9</td>
<td>–1.1</td>
</tr>
</tbody>
</table>

The proportion of patients with prolactin elevations ≥ 5× upper limit of normal (ULN) was 2.8% for LATUDA-treated patients versus 1.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥ 5× ULN was 5.7% for LATUDA-treated patients versus 2.0% for placebo-treated female patients. The proportion of male patients with prolactin elevations > 5× ULN was 1.6% versus 0.6% for placebo-treated male patients.

In the uncontrolled, long-term studies (primarily open-label extension studies), LATUDA was associated with a median change in prolactin of –0.9 ng/mL at week 24 (n=357), –5.3 ng/mL at week 36 (n=390) and –2.2 ng/mL at week 52 (n=307).

The following adverse reactions are discussed in more detail in other sections of this monograph.

5.7 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/mm³) should discontinue LATUDA and have their WBC followed until recovery.

5.8 Orthostatic Hypotension and Syncope
LATUDA may cause orthostatic hypotension, perhaps due to its α1-adrenergic receptor antagonist action. The incidence of orthostatic hypotension and syncope events from short-term, placebo-controlled studies was 1.7% for LATUDA incidence placebo (Incidence): orthostatic hypotension [0.3% (5/1508), 0.1% (1/708)] and syncope [0.1% (2/1508), 0.0% (0/708)]. Assessment of orthostatic hypotension was defined by 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 positions. In short-term clinical trials, orthostatic hypotension 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.

Orthostatic vital signs should be monitored in patients who are vulnerable to hypotension (e.g., dehydration, hypovolemia, and treatment with antihypertensive medications), and in patients with known cardiovascular disease (e.g., heart failure, history of myocardial infarction, ischemia, or conduction abnormalities), or cerebrovascular disease.

5.9 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.

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

5.10 Potential for Cognitive and Motor Impairment
LATUDA, like other antipsychotics, has the potential to impair judgment, thinking or motor skills.

In short-term, placebo-controlled trials, 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. In these short-term trials, somnolence included: hypersomnia, hypersomnolence, sedation and somnolence.

Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

5.11 Body Temperature Regulation
Disruption of the body’s ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing LATUDA for patients who will be experiencing conditions that may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to environmental heat stress. (See Patient Counseling Information [17.9]).

5.12 Suicide
The possibility of a suicide attempt is inherent in psychotic illness and close supervision of high-risk patients should accompany drug therapy. Prescriptions for LATUDA should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

In treating, placebo-controlled studies in patients with schizophrenia, the incidence of treatment-emergent suicidal ideation was 0.4% (6/1508) for LATUDA-treated patients compared to 0.8% (6/708) on placebo. No suicide attempts or completed suicides were reported in these studies.

5.13 Dysphagia
Esophageal dysmotility and aspiration have been associated with antipsychotic drugs use. Aspiration pneumonia is a common cause of morbidity and mortality among elderly patients, in particular those with advanced Alzheimer’s dementia. LATUDA and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.
5.14 Use in Patients with Concomitant Illness

Clinical experience with LATUDA in patients with certain concomitant illnesses is limited. See Clinical Pharmacology (12.2).

Patients with Parkinson’s Disease or Dementia with Lewy Bodies are reported to have an increased sensitivity to antipsychotic medication. Manifestations of this increased sensitivity include confusion, obtundation, postural instability with frequent falls, extrapyramidal symptoms, and clinical features consistent with the neurologic malignant syndrome.

LATUDA has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical trials. Because of the risk of orthostatic hypotension with LATUDA, caution should be observed in patients with known cardiovascular disease [see Warnings and Precautions (5.8)].

6 ADVERSE REACTIONS

The following adverse reactions are discussed in more detail in other sections of the labeling:

- Use in Elderly Patients with Dementia-Related Psychosis [see Boxed Warning and Warnings and Precautions (5.1)]
- Cardiac Adverse Reactions, Including Stroke [see Warnings and Precautions (5.2)]
- Neuroleptic Malignant Syndrome [see Warnings and Precautions (5.3)]
- Tardive Dyskinesia [see Warnings and Precautions (5.4)]
- Hyperglycemia and Diabetes Mellitus [see Warnings and Precautions (5.5)]
- Hyperprolactinemia [see Warnings and Precautions (5.6)]
- Leukopenia, Neutropenia, and Agranulocytosis [see Warnings and Precautions (5.7)]
- Orthostatic Hypotension and Syncope [see Warnings and Precautions (5.8)]
- Seizures [see Warnings and Precautions (5.9)]
- Potential for Cognitive and Motor Impairment [see Warnings and Precautions (5.10)]
- Body Temperature Regulation, [see Warnings and Precautions (5.11)]
- Suicide [see Warnings and Precautions (5.12)]
- Dysphagia [see Warnings and Precautions (5.13)]

6.1 Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in clinical practice.

The information below is derived from a clinical study database for LATUDA consisting of 2905 patients with schizophrenia exposed to one or more doses with a total experience of 9853 patient-years. Of these patients, 1508 participated in short-term, placebo-controlled schizophrenia studies with doses of 20 mg, 40 mg, 80 mg, 120 mg or 160 mg once daily. A total of 769 LATUDA-treated patients had at least 24 weeks and 371 LATUDA-treated patients had at least 52 weeks of exposure.

Adverse events during exposure to study treatment were obtained by general inquiry and voluntarily reported adverse experiences, as well as results from physical examinations, vital signs, ECGs, weights and laboratory investigations. Adverse experiences were recorded by clinical investigators using their own terminology. In order to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.

The following tables are based on the short-term, placebo-controlled premarketing studies for schizophrenia in which LATUDA was administered at daily doses ranging from 20 to 160 mg (n=1508).

### 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, akathisia, nausea, and parkinsonism.

### Adverse Reactions Associated with Discontinuation of Treatment

A total of 9.5% (143/1508) LATUDA-treated patients and 9.3% (66/708) 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

Adverse reactions associated with the use of LATUDA (incidence of 2% or greater, rounded to the nearest percent and LATUDA incidence greater than placebo) that occurred during acute therapy (up to 6 weeks in patients with schizophrenia) are shown in Table 5.

### Table 5: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=708)</th>
<th>All LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>Vomiting</td>
<td>6</td>
<td>8</td>
</tr>
<tr>
<td>Dysepisia</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Salivary Hypersecretion</td>
<td>&lt;1</td>
<td>2</td>
</tr>
</tbody>
</table>

### Dose-Related Adverse Reactions

In pooled data from the short-term, placebo-controlled, fixed-dose studies, there were no dose-related adverse reactions (greater than 5% incidence) in patients treated with LATUDA across the 20 mg/day to 160 mg/day dose range. However, the frequency of akathisia increased with dose up to 120 mg/day (5.6% LATUDA 20 mg, 10.7% LATUDA 40 mg, 12.5% LATUDA 80 mg, 22.0% 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.

### Extrapyramidal Symptoms

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 restlessness, 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 7.

### Table 6: Incidence of EPS Compared to Placebo

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=799) (%)</th>
<th>LATUDA (N=1508) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dystonia***</td>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>Akathisia</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Dystonia**</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Restlessness</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

* Dystonia includes adverse event terms: dystonia, oculogyric crisis, oromandibular dystonia, tongue spasm, torticollis, and trismus

** Parkinsonism includes adverse event terms: bradykinesia, cogwheel rigidity, drooling, extrapyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor

In the short-term, placebo-controlled schizophrenia studies, data was objectively collected on the Simpson Angus Rating Scale for extrapyramidal symptoms (EPS), the Barnes Akathisia Scale (for akathisia) and the Abnormal Involuntary Movement Scale (for dyskinesias). The mean change from baseline for LATUDA-treated patients 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%) and the SAS (LATUDA, 5.0%; placebo, 2.3%).
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.

In the short-term, placebo-controlled clinical trials, 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.

Other Adverse Reactions Observed During the Premarketing Evaluation of LATUDA
Following is a list of adverse reactions reported by patients treated with LATUDA at multiple doses of ≥ 20 mg once daily during any phase of a study within the database of 2905 patients. 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 5 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); 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, dysarthria 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

7 DRUG INTERACTIONS
7.1 Potential for Other Drugs to Affect LATUDA
LATUDA is predominantly metabolized by CYP3A4. LATUDA should not be used in combination with strong inhibitors or inducers of this enzyme [see Contraindications (4)] and should be limited when used in combination with moderate inhibitors of CYP3A4 [see Dosage and Administration (2.4)]. No dose adjustment is needed with concomitant use of lithium (see Figure 1).

Figure 1: Impact of Other Drugs on LATUDA Pharmacokinetics

7.2 Potential for LATUDA to Affect Other Drugs
No adjustment is needed on the dose of lithium, or substrates of P-gp or CYP3A4 when coadministered with LATUDA (Figure 2).

Figure 2: Impact of LATUDA on Other Drugs

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Teratogenic Effects
Pregnancy Category B
LATUDA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects
Neonates exposed to antipsychotic drugs during the trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.

Safe use of LATUDA during pregnancy or lactation has not been established; therefore, use of LATUDA in pregnancy, in nursing mothers, or in women of childbearing potential requires that the benefits of treatment be weighed against the possible risks to mother and child.

Animal Data
No adverse developmental effects were seen in a study in which pregnant rats were given LATUDA during the period of organogenesis and continuing through weaning at doses up to 10 mg/kg/day; this dose is approximately half of the MRHD based on body surface area.

No teratogenic effects were seen in studies in which pregnant rats and rabbits were given LATUDA during the period of organogenesis at doses up to 25 and 50 mg/kg/day, respectively. These doses are 1.5- and 6-fold, respectively, the maximum recommended human dose (MRHD) of 160 mg/day based on body surface area.

8.3 Nursing Mothers
LATUDA was excreted in milk of rats during lactation. It is not known whether LATUDA or its metabolites are excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, considering risk of drug discontinuation to the mother.

8.4 Pediatric Use
Safety and effectiveness in pediatric patients have not been established.

8.5 Geriatric Use
Clinical studies of LATUDA in the treatment of schizophrenia 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 [see Clinical Pharmacology (12.3)]. No dose adjustment is necessary in elderly patients (Figure 2).

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 [see Boxed Warning].

8.6 Other Patient Factors
The effect of intrinsic patient factors on the pharmacokinetics of LATUDA is presented in Figure 3.
10.1 Human Experience
In premarketing clinical studies involving 2905 patients, accidental or intentional overdose 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.

10.2 Management of Overdosage
Consult a Certified Poison Control Center for up-to-date guidance and advice. There is no specific antidote to LATUDA, therefore, appropriate supportive measures should be instituted and close medical supervision and monitoring should continue until the patient recovers.

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.