SUBTHRESHOLD BIPOLARITY, LOW-DOSE LITHIUM, AND NON-DRUG OPTIONS FOR COMPLEX DEPRESSIONS
BIPOLAR DISORDER CHALLENGES

Subthreshold Bipolarity, Low-Dose Lithium, and Non-Drug Options for Complex Depressions

JAMES PHELPS, MD

James Phelps, MD, is Director of the Mood Disorders Program at Samaritan Mental Health in Corvallis, Oregon. He is the Bipolar Disorder Section Editor for Psychiatric Times and the author of A Spectrum Approach to Mood Disorders: Not Fully Bipolar But Not Unipolar—Practical Management.

This Supplement examines 3 problems in bipolar disorder management and suggests respective changes in clinical practice:

1. Clinicians are using different diagnostic approaches. The result is different diagnoses for the same patient, and different treatment recommendations.
2. Some clinicians avoid lithium despite accumulating data indicating a specific anti-suicide effect from even very low doses.
3. Non-pharmacologic treatments are often overlooked in favor of medications.

Diagnostic differences

Given the same patient history, psychiatrists’ diagnostic interrater reliability is comparable to that found in other fields of medicine.1-3 But an online quiz from Psychiatric Times suggests we are not gathering the same data.4 In that survey, 256 clinicians responded to the question “How do you approach bipolar diagnosis?” The Figure shows their responses.

As you can see, roughly half of responding clinicians assess only the DSM “A” criteria (elevated, expansive or irritable mood, with increased energy): if not found, no further examination of bipolar symptoms is done. That means there are no queries about phases of self-confidence or increased social activity or spending or risk, etc. Granted, if the A criteria are absent, according to the DSM system, then bipolar disorder cannot be diagnosed—so this is efficient and technically correct.

One-quarter of responding clinicians assess all the DSM criteria and interpret them in yes/no fashion, whereas one-fifth interpret them dimensionally using a spectrum view of bipolarity, discussed further below. The last group uses the Bipolarity Index, also described below.

Like Greek mythology’s Jason navigating between Scylla and Charybdis (the original “rock and a hard place” depicted on the cover of this supplement), clinicians must find the narrow passage between overdiagnosis, with its risks of stigmatization and sometimes use of high-risk treatments; and underdiagnosis, where the default diagnosis of Major Depression can lead to antidepressants, mixed states, and suicidality. Blending a categorical DSM approach with a dimensional spectrum approach may help find that middle ground.

A spectrum approach to mood diagnosis: concerns and advocates

The Chair and Vice-Chair of Washington University at St. Louis’ Department of Psychiatry have warned of risks associated with a spectrum approach to bipolar diagnosis.5 They note:

• It is clinically difficult to define the border between a variant of normal behavior and the behaviors that are associated with “subthreshold bipolar disorder.”
• These behaviors might reflect underlying personality, anxiety, substance abuse, or reactions to psychosocial stressors.
• Labeling such behaviors as “bipolar spectrum” suggests that the brains of affected people have a milder form of the pathology that exists in the brains of persons with major bipolar disorder. This may or may not be true, but it suggests that treatments for bipolar I disorder are appropriate for these milder symptoms.

Most importantly, the Chair and Vice-Chair emphasize the absence of evidence that treatments for “major bipolar” (their term) actually work for patients with subthreshold bipolarity—treatments with sometimes dangerous adverse effects.

These valid concerns have strong implications for treatment decisions that we clinicians are making all the time, and should not be ignored. At the same time, many prominent mood specialists have advocated shifting to a spectrum approach to diagnosis of mood disorders, including:

• The chairman of DSM-5
• The head of the NIMH research group on bipolar disorders
• The principal investigator of the largest bipolar research program ever conducted—the STEP-BD
• The chairman of the International Society for Bipolar Disorders’ (ISBD) Committee on Diagnosis

FIGURE 1. Approaches to bipolar diagnosis (Bipolarity Index defined in text below)

<table>
<thead>
<tr>
<th>Approach</th>
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<td>Assess DSM A criteria (only, unless +)</td>
<td>45%</td>
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<td>Assess DSM A and B criteria (all cases)</td>
<td>26%</td>
</tr>
<tr>
<td>Assess DSM A and B criteria, interpret dimensionally</td>
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3.0.16,17 Ms. Carter’s CIDI score was 4, which indicates low risk of bipolar disorder, and supports the earlier diagnosticians. If she has had some past or present symptoms that suggest a degree of hypomania; if she has had a suggestive adverse response to an antidepressant; or if several antidepressants failed to improve her depression, then take another step: get more information. Additional markers of bipolarity can be assessed, markers that do not appear in the DSM, including family history, age of onset of depressions, recurrence, post-partum onset, and hypomaniac/ manic-like reactions to antidepressants. These markers shift the probability that a patient’s depression has a bipolar component. Along with the patient’s symptoms, they constitute the Bipolarity Index, a quantitative version of which has been validated.13,14

One way to gather data on these non-manic markers is presented in Case 1. Case 2 (page 5) illustrates a risk of ignoring them, and the potential for low-dose lithium to bridge the gap between unipolar and bipolar-based treatment approaches when clinicians don’t agree. The final section of this Supplement (page 6) reviews the literature on several non-pharmacological treatments that broaden the range of low-risk treatment options, perhaps thereby decreasing the concern that a spectrum approach to mood diagnosis leads straight to consideration of high-risk medications. And perhaps this may increase the distance between our Scylla and our Charybdis.

How to reconcile these opposite views?
First, recognize the false dichotomy: the DSM categorical system can be used with a spectrum approach. If a patient clearly meets DSM criteria for bipolar disorder, make a DSM-based diagnosis. But when she doesn’t, yet has some past or present symptoms that suggest a degree of hypomania; if she has had a suggestive adverse response to an antidepressant; or if several antidepressants failed to improve her depression, then take another step: get more information. Additional markers of bipolarity can be assessed, markers that do not appear in the DSM, including family history, age of onset of depressions, recurrence, post-partum onset, and hypomaniac/manic-like reactions to antidepressants. These markers shift the probability that a patient’s depression has a bipolar component. Along with the patient’s symptoms, they constitute the Bipolarity Index, a quantitative version of which has been validated.13,14

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Not Bipolar, But Not Unipolar Either: Case #1

Ms. Carter,” 39-years-old, presents to our primary care consultation program with depression and anxiety. Her previous charted diagnoses are shown in Table 1:

<table>
<thead>
<tr>
<th>TABLE 1. Ms. Carter’s previous charted diagnoses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychology graduate trainee</td>
</tr>
<tr>
<td>Psychology supervisor</td>
</tr>
<tr>
<td>4th Year psychiatry resident</td>
</tr>
</tbody>
</table>

“Ms. Carter, you do not have ‘bipolar disorder,’ but you don’t have plain depression either, because you have… (cite the positive non-manic markers from the Bipolarity Index).”

But our liaison’s standard interview also includes a questionnaire that elicits data on non-manic markers of bipolarity.

Table 2 shows Ms. Carter’s responses on the (validated18) family history screener:

Table 3 shows her responses regarding the rest of the Bipolarity Index features. (You can download a version of this questionnaire, complete with Bipolar Spectrum Diagnostic Scale, a validated tool akin to the Mood Disorders Questionnaire. Google MoodCheck Bipolar.)19

Ms. Carter did not have the classic age of onset for bipolar disorder at age 15–20. She has not had antidepressant loss of response nor a gambling problem, but she has had perimenstrual worsening (these 3 findings are weak markers). She had a post-partum depression and—among the strongest indicators of bipolarity—she experienced antidepressant-associated insomnia, agitation, and irritability. As one could explain to her, “Ms. Carter, you do not have ‘bipolar disorder,’ but you don’t have plain depression either, because you have… (cite the positive non-manic markers from the Bipolarity Index).”

Gary Sachs, principal investigator for the STEP-BD (Systematic Treatment Enhancement Program for Bipolar Disorders), affirmed an interviewer’s characterization of the Bipolarity Index: “It’s not a categorical yes or no… but rather ‘to what extent are you bipolar?’” Dr. Sachs replied: “yes, and we’re not looking to replace the DSM with it;… it’s just that we are able to approach it more as a continuous issue, rather than as a black-and-white yes/no.”

By DSM criteria, Ms. Carter does not have bipolar disorder. But per the Bipolarity Index, she has multiple non-manic markers.

Now what to do?

Treatment recommendations
Ms. Carter’s chart indicates that she has had 3 prior antidepressant trials. The questionnaire shown in Table 3 shows that at least 1 of

In our variation of the Collaborative Care Model,15 an in-clinic liaison charts the patient’s replies to structured interview questions, and responses to a scripted bipolar diagnostic interview, the CIDI 3.0.16,17 Ms. Carter’s CIDI score was 4, which indicates low risk of bipolar disorder, and supports the earlier diagnosticians.
BIPOLAR DISORDER CHALLENGES

those trials was associated with insomnia, agitation, and irritability. This led the consultant to recommend a trial of lamotrigine for Ms. Carter’s depression and anxiety, on the presumption that these symptoms were driven by at least some degree of bipolarity.

If Ms. Carter had never previously tried an antidepressant, this would have been a much more difficult decision. In such cases, one option is to emphasize psychotherapy first, including the non-medication mood-stabilizing approaches that have antidepressant effects. These are discussed in Section 3 (page 6) of this Supplement.

Psychoeducation about non-manic versions of bipolar disorders (eg, PsychEducation.org\textsuperscript{20}) can also help patients participate in an informed shared decision-making approach.

Why lamotrigine? The 2018 CANMAT guidelines include a thoughtful summary of the lamotrigine literature while including it as first line for bipolar depression. Skeptics are referred to their summary, which concludes:

“…Taken together, we believe these data justify at least a Level 2 rating. . . Lamotrigine has also demonstrated efficacy in mainte-

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**TABLE 2. Family history by questionnaire**

<table>
<thead>
<tr>
<th>Please indicate whether any of your (blood) relatives have had any of these concerns:</th>
<th>Grandparents</th>
<th>Parents</th>
<th>Aunts/Uncles</th>
<th>Brothers/Sisters</th>
<th>Children</th>
</tr>
</thead>
<tbody>
<tr>
<td>Suicide</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Alcohol/drug problems</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Schizophrenia</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Depression problems</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Manic, bipolar, schizoaffective</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>Anxiety problems</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>ADD or ADHD</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

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**TABLE 3. Non-manic markers of the Bipolarity Index, by questionnaire**

<table>
<thead>
<tr>
<th>How old were you when you first were depressed (if so)? (circle one)</th>
<th>As long as I can remember</th>
<th>Grade school</th>
<th>Before age 15</th>
<th>15–19</th>
<th>20–25</th>
<th>25–30</th>
<th>Over 30</th>
</tr>
</thead>
<tbody>
<tr>
<td>How many episodes of depression have you had?</td>
<td>Zero</td>
<td>One</td>
<td>2–4</td>
<td>5–6</td>
<td>10 or more</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Has an antidepressent you took worked at first, then stopped working?</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ever had a problem with gambling?</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Do you have a clear worsening of mood symptoms in the week before a menstrual cycle?</td>
<td>No</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Did you have an episode after giving birth?</td>
<td>No</td>
<td>Within 6 months</td>
<td>Within 2 months</td>
<td>Within 2 weeks</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Are your moods much different at different times of year?</td>
<td>No effect of time of year</td>
<td>Yes, seasonal shifts</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>When you are depressed, what happens to your energy?</td>
<td>Nothing</td>
<td>It varies a lot</td>
<td>Very low</td>
<td>Extremely low, can hardly move</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In episodes, have you lost contact with reality? (delusions, voices, people thought you were odd)</td>
<td>No</td>
<td>Yes</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>How many antidepressants have you tried, if any?</td>
<td>None</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>More than 3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Have antidepressants ever caused: (circle all that apply)</td>
<td>Excessive energy</td>
<td>Severe insomnia</td>
<td>Agitation</td>
<td>Irritability</td>
<td>Racing thoughts</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis—or Lithium Anyway? Case #2

Mr. Jackson,” 65-years-old, called his primary care provider and described feelings of sadness and anxiety for the last several weeks. He was seen several days later and told of suicidal thoughts.

A psychiatric consultation was arranged on an urgent basis. Significant history includes his having stopped sertraline after several years use because he finally tired of associated sexual dysfunction. When his mood began to plummet, Mr. Jackson restarted sertraline. Despite taking the same 50 mg dose to which he’d responded well not long before, re-exposure elicited agitation, irritability, racing thoughts with difficulty concentrating, and difficulty falling asleep and staying asleep. These symptoms persisted despite stopping the sertraline after 3 doses. His low mood and anhedonia have persisted.

Diagnosis and treatment
The consultant’s differential included depression with mixed features versus bipolar depression with concurrent manic symptoms—even though Mr. Jackson had not previously had manic symptoms.

He was a highly regarded professional with hyperthymic traits, such as remarkable productivity, many friends and associates, and sleeping only 4–6 hours nightly for years. A 3rd-degree relative had re-exposure elicited agitation, irritability, racing thoughts with difficulty concentrating, and difficulty falling asleep and staying asleep. These symptoms persisted despite stopping the sertraline after 3 doses. His low mood and anhedonia have persisted.

Lamotrigine and Folic Acid: A Re-Analysis
A side note on lamotrigine: the consultant checked to see if Ms. Carter was taking a folic acid supplement. Why? Because a recent study suggested that folic acid could interfere with response to lamotrigine. A subsequent analysis of the same data showed that folic acid was not lowering lamotrigine blood levels. Rather, it may have an effect through folate’s participation in the one-carbon cycle of methionine and homocysteine, affecting glutathione (an antioxidant) production. Genotype for the MTHFR polymorphism did not affect this apparent interaction, suggesting that supplementation with L-tetrahydrofolate instead of folic acid would not avoid this problem. The authors emphasize that these results need replication with a larger sample, but for now have recommended that patients taking lamotrigine not take folic acid. Obviously, someone who is taking both and responds well to lamotrigine need not change course; but non-response to lamotrigine might warrant a later re-try off folic acid.
better for about 2 weeks, but then worsened again.

Escitalopram was increased to 20 mg daily. The next day, the patient experienced racing thoughts, and restlessness and agitation for about 10 hours. But these symptoms then went away and he was left with his usual depressed and anxious/agitated state. Because these symptoms disappeared quickly, escitalopram was continued. Over the next 2 months, depression did not worsen but he became more agitated and angry, yelling more at his wife, and reporting continued suicidal thoughts.

Mr. Jackson was referred for electroconvulsive therapy (ECT) and had 9 sessions without a change in his symptoms. Escitalopram, which had been continued during the ECT, was then augmented with bupropion 150 mg, which was increased after a week to 300 mg daily.

Two weeks later Mr. Jackson hanged himself in his garage.

Low-dose lithium
Was Mr. Jackson experiencing a treatment-resistant Major Depressive Disorder? Or was it a mixed state that may have been worsened by antidepressants? This distinction is no easier looking backwards than it was at the time. But a middle path may have been overlooked.

Lithium has now been repeatedly associated with decreased suicide risk, even in microdoses found in some municipal water supplies. A remarkably linear relationship between lithium’s concentration in drinking water and suicide rate—the higher the lithium, the lower the rate—was shown in various regions in Japan, for example.\(^{31}\) (31 mcg/L has been suggested as the lowest potentially active level.\(^{30}\)) These data reinforce those from epidemiologic studies, (eg, all patients treated with lithium or other mood stabilizers in Denmark,\(^{31}\) and clinical trials).\(^{32}\)

Thus, one option for patients like Mr. Jackson who present with depression, who don’t respond to initial treatments, and who experience suicidal ideation, is to augment with low-dose lithium—presuming no contraindications. Whether the primary diagnosis is depression or bipolar disorder—or PTSD or GAD or borderline—does not matter. Low-dose lithium means: start with 150 mg capsule. Increase only if no side effects. Increase weekly until improvement (keep that dose) or side effects (back down one step) or 600 mg nightly. Check a level 1 week after dose is steady. Watch for emerging hypothyroidism, especially in women, those with a family history of thyroid problems, and those with a starting TSH over 2.5. Repeat a TSH as early as 1.5–2 months if several such factors are present, or if depression seemed to improve then worsened (even in a few weeks).

[This case is an amalgam of 3 patients, including one of the author’s, with similar presentations and outcomes; a published case supports the symptom evolution.]

Non-Medication Treatments for Bipolar Disorders: A Literature Review

MUltiple bipolar-specific psychotherapies have been shown in randomized trials to be superior to active control conditions. Shared ingredients include psychoeducation, self-monitoring of mood, and emphasis on relapse prevention. Perhaps the most important single ingredient, recently isolated in a small but striking pilot study, is sleep regularity. This can be promoted through careful management of light, darkness, and regular bed- and rise-times.

Light therapies
Don’t leap to the light box. First, consider a dawn simulator—a simple device that turns on a bedside light gradually, “simulating dawn,” at a regular time every morning.\(^{33}\) Simulators are cheaper and easier to use than a light box. In a cross-over comparison of dawn simulators and light boxes for seasonal affective disorder, the light box was found to be preferable among the subgroup of patients with more severe depression, but otherwise the ease of use of the dawn simulator was preferred.\(^{34}\) Unfortunately, to date we have no randomized trial of these simple devices in patients with bipolar disorder, let alone subthreshold bipolarity; all the studies have been done in seasonal affective disorders. But these devices are inexpensive and harmless.

This an example of a much broader issue in psychiatric decision-making: should tolerability and short/long-term safety or efficacy guide the selection of a treatment? This too is a spectrum issue. When symptoms carry significant risk (to life, relationships, finances, jobs), treatments with rapid action and high probability of benefit are the top options. But when patients face symptoms that have occurred and will continue for years, and treatments that will likewise continue for a long time, tolerability may become one of the top considerations.\(^{35}\) For treatment with no known risks and little or no cost, how much evidence for efficacy is needed? These are questions for patient/clinician-shared decision-making.\(^{36}\) At minimum, using a dawn simulator strongly reinforces the importance of sleep regularity (more on this below).

By comparison, treating bipolar depression with bright light therapy using a standard light box now has a randomized trial with strong evidence for efficacy.\(^{37}\) Caution with bright light treatment in bipolar depression had been suggested; in a pilot study in bipolar disorders, 5 of 9 patients went into a mixed state in association with conventional morning timing. However, 4 of those 5 got a good outcome when switched to 15 minutes at midday.\(^{38}\) This led to the larger trial, just recently published by Dr. Dorothy Sit and colleagues,\(^{37}\) in which adjunctive midday bright light therapy produced remission from bipolar depression in 68% of patients, versus 22% of controls. You read that right: 68% remission, with adjunctive light therapy. Macular degeneration or a family history thereof are contraindications, as are some rarely used medications.\(^{39}\)
Dark therapies

If light is an antidepressant, and antidepressants can induce cycling, might darkness be a mood stabilizer?

This was affirmed in a striking case report from the NIMH, in which a patient with years of depressions and manias was treated with no medications at all and essentially stopped cycling. Treatment was 14 hours of darkness nightly, reduced after initial improvement to 10 hours per night, which kept him well for over a year in this report.40

But patients don’t want to give up their light at night. As clinicians know, they are particularly reluctant to give up their electronic devices: TV, computers, tablets, and phones, all of which emit a very bright light. However, not all wavelengths of light are created equal; blue light alone is the primary determinant of circadian rhythm.41, 42

If blue light equals circadian darkness, then the absence of blue light—even in the presence of all the other wavelengths—ought to be a circadian darkness, akin to dark night. So, can one create a “virtual darkness” by blocking blue light? Sure enough: a pair of amber safety glasses can preserve normal melatonin production even in a fully lit environment.43 (An inexpensive version made for blue-laser welding costs less than $9.0044). Imagine the curves in this important, striking study: in darkness, a normal 8-hour melatonin rise/fall.

Weeks later, when the same subjects were kept awake all night “simulating shift work” under electric lights, their melatonin curve was basically flat, almost zero production. Then weeks later, the same subjects again did shift work simulation all night in a lit environment, with blue light blocked by the amber lenses. On the latter night, their melatonin curve looks just like the first one43.

So: if darkness can be a mood stabilizer, as shown by the NIMH case, could virtual darkness be an effective anti-manic (and by extension, function as a mood stabilizer)? After a 20-patient case series suggested this might work,45 a Norwegian team demonstrated a very strong anti-manic effect following the NIMH darkness protocol but using amber lenses instead of real darkness.46 Patients hospitalized with mania who were randomized to blue-blocking lenses had precipitous decline in their Young Mania Rating Scale scores relative to the group wearing control lenses. This study was dubbed one of three “best papers of 2017” by the International Society for Bipolar Disorders.47

An even more practical application of blue-blocking lenses was just published, showing increased melatonin production and sleepiness in adolescents wearing amber lenses for 3 hours before bedtime. One week of this regimen was associated with decreased daytime sleepiness.48 In my experience, 2–3 hours is the longest that can be used in patients with bipolarity, including induction of mixed states and suicide risk.

Other helpful tools include no-blue nightlights and no-blue LEDs from lowblueights.com. (Computer programs like Night Shift (Apple) or f.lux (PC) help but do not eliminate bright blue light.49) Like the dawn simulator, these tools have very little evidence for efficacy in bipolar disorders (except for the prize-winning randomized trial of amber lenses), and no evidence in mid-spectrum mood disorders, where very few treatments have been studied. But they are inexpensive and ostensibly harmless, so like the dawn simulator, they deserve consideration in patient/clinician shared decision-making.50

These tools are particularly helpful when a clinician needs more time, or more data, to determine “how bipolar is this patient?” They can be employed while still in doubt (though there was one patient in the Norwegian trial who became acutely depressed using the amber lenses, so caution is still warranted. Fortunately, this is a treatment that can be immediately discontinued).

Cognitive therapy for insomnia, bipolar version: CBT-IB

Simply teaching patients extensively about bipolar disorder has been shown to reduce relapse rates substantially50 and sustainedly.51 So a California team that set out to study a simple CBT-based therapy was very bold when they used psychoeducation as their control condition. Yet compared to this very active control, their new bipolar-specific CBT cut the rate of relapse into depression by half and relapse into hypomania/mania more than 10-fold (adjunctive to ongoing medications).52 Ingredients in this therapy include standard CBT-I (sleep hygiene, sleep restriction; wind-down and wake-up routines; “behavioral experiments to allow the patient to experience the energy-generating effects of activity” (CBT-style motivational interviewing, laced throughout the treatment); and CBT around sleep beliefs and bedtime worry. A 4-page concise description is available online.53

Though only a pilot study, the data are striking. The method is relatively simple, within reach of many CBT therapists, some of whom may already offer CBT-I; if not, they can adopt the all-inclusive CBT-I “app” from the Stanford Sleep Lab, CBT-I Coach, which makes CBT-I vastly easier for the therapist as well as for the patient.54 Some patients can adopt many of these behavioral changes on their own once they understand the importance of managing light, darkness, and sleep. This emphasis on behavior change is an important intervention for all patients with bipolar disorder; but it is so simple, so safe, and so “do-able” that it can be used in patients with mid-spectrum mood disorders even while we wait for clinical trial data in such patients. One preliminary such study has already been completed, comparing quetiapine and Social Rhythm Therapy (another psychotherapy developed originally for bipolar disorders with an emphasis on regular rhythms, particular sleep) in patients with subthreshold bipolarity. Although not powered to show superiority, in this preliminary study, outcomes were equal (per clinicaltrials.gov; awaiting publication).55

Conclusion

Gathering all the data relevant to the differential diagnosis of depression would allow us to at least begin with the same information. Tools such as MoodCheck and the Bipolarity Index can help gather and record these data. These variables—family history, age of onset, course of illness, response to treatment—allow for a mid-spectrum version of depression: “You don’t have bipolar disorder, but you don’t have plain depression either because you have x, y, z non-manic bipolar markers”.

This diagnosis does not lead straight to high-risk treatments. It leads some patients instead to lamotrigine, low-dose lithium, dawn simulators and amber lenses; and bipolar-specific CBT-I and bright light therapy. From there one can consider more aggressive treatments for depression, weighing the risks of antidepressants in patients with bipolarity, including induction of mixed states and suicidality, versus the risks our colleagues at Washington University have warned about: those that accompany medications used in Bipolar I. A spectrum approach creates more room between psychiatry’s Scylla and Charybdis.
LATUDA helps adult patients with bipolar depression experience more of life’s everyday moments.

INDICATIONS
LATUDA is indicated for monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) and adjunctive treatment with lithium or valproate in adult patients with bipolar depression.

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.

The efficacy of LATUDA in the treatment of mania associated with bipolar disorder has not been established.

IMPORTANT SAFETY INFORMATION FOR LATUDA
Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adults in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors.

Contraindications: LATUDA is contraindicated in the following:
- Known hypersensitivity to lurasidone HCl or any components in the formulation. Angioedema has been observed with lurasidone
- Strong CYP3A4 inhibitors (e.g., ketoconazole)
- Strong CYP3A4 inducers (e.g., rifampin)
Bipolar depression is different than other types of depression.

LATUDA provides proven antidepressant efficacy in patients with bipolar depression.

- **Efficacy established** in adults and in pediatric patients (10 to 17 years) with bipolar depression
  - In adult studies, LATUDA monotherapy and adjunctive therapy with lithium or valproate were superior to placebo in the reduction of Montgomery-Åsberg Depression Rating Scale (MADRS) scores at Week 6
  - In the pediatric study, LATUDA monotherapy was superior to placebo in the reduction of Children's Depression Rating Scale, Revised (CDRS-R) scores at Week 6
- **Safety and tolerability** established in multiple bipolar depression studies, including short-term pivotal studies and longer-term, open-label extension studies
- **Once-daily dosing**, taken with food (at least 350 calories)

Cerebrovascular Adverse Reactions, Including Stroke: In clinical trials, elderly patients with dementia randomized to risperidone, aripiprazole, and olanzapine had a higher incidence of stroke and transient ischemic attack, including fatal stroke. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic Malignant Syndrome (NMS): NMS is a potentially fatal symptom complex reported with administration of antipsychotic drugs. Clinical signs of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. Manage NMS with immediate discontinuation of antipsychotic drugs, including LATUDA, intensive symptomatic treatment and monitoring.

Learn more at LATUDehcp.com

Please see additional Important Safety Information, including Boxed Warning, and Brief Summary of Prescribing Information on adjacent pages.
Tardive Dyskinesia (TD): The risk of developing TD (a syndrome of abnormal involuntary movements) and the potential for it to become irreversible are believed to increase as the duration of treatment and total cumulative dose of antipsychotic increase. The syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses or may even arise after discontinuation of treatment. The syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn.

Metabolic Changes: Atypical antipsychotic drugs have caused metabolic changes, including:

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

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.

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

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

Leukopenia, Neutropenia, and Agranulocytosis: Leukopenia/neutropenia has been reported with antipsychotics. Agranulocytosis (including fatal cases) has been reported with other agents in the class. Monitor complete blood count in patients with a pre-existing low white blood cell count (WBC)/absolute neutrophil count (ANC) or a history of drug-induced leukopenia/neutropenia. Discontinue LATUDA at the first sign of a decline in WBC in the absence of other causative factors.

Orthostatic Hypotension and Syncope: Atypical antipsychotics cause orthostatic hypotension and syncope. Generally, the risk is greatest at the beginning of treatment and when increasing dose. Monitor patients vulnerable to hypotension and those with cardiovascular and cerebrovascular disease.

Falls: Antipsychotics may cause somnolence, postural hypotension, or motor and sensory instability, which may lead to falls, causing fractures or other injuries. For patients with disease, conditions, or medications that could exacerbate these effects, complete fall risk assessments when initiating treatment and recurrently during therapy.

Seizures: LATUDA should be used cautiously in patients with a history of seizures or with conditions that lower seizure threshold.

Potential for Cognitive and Motor Impairment: Patients should be cautioned about operating hazardous machinery, including motor vehicles, until they are reasonably certain that therapy with LATUDA does not affect them adversely.

Body Temperature Regulation: Use LATUDA with caution in patients who may experience conditions that increase body temperature (e.g., exercising strenuously, exposure to extreme heat, concomitant medication with anticholinergic activity, or being subject to dehydration).

Dysphagia: Antipsychotics, including LATUDA, have been associated with esophageal dysmotility and aspiration, and should be used with caution in patients at risk for aspiration pneumonia.

Most Commonly Observed Adverse Reactions: The most commonly observed adverse reactions (≥5% incidence and at least twice the rate of placebo) for LATUDA:

- In adult patients: akathisia, extrapyramidal symptoms, and somnolence
- In pediatric patients (10 to 17 years): nausea, weight increase, and insomnia

To report SUSPECTED ADVERSE REACTIONS, contact Sunovion Pharmaceuticals Inc. at 877-737-7226 or FDA at 1-800-FDA-1088 (www.fda.gov/medwatch).

INDICATIONS
LATUDA is indicated for monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression) and adjunctive treatment with lithium or valproate in adult patients with bipolar depression.

Please see Brief Summary of Prescribing Information, including Boxed Warning, on adjacent pages.

INDICATIONS AND USAGE
LATUDA is indicated for:
- Treatment of adult and adolescent patients (13 to 17 years) with schizophrenia.
- Monotherapy treatment of adult and pediatric patients (10 to 17 years) with major depressive episode associated with bipolar I disorder (bipolar depression).
- Adjunctive treatment with lithium or valproate in adult patients with major depressive episode 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, voriconazole, mibefradil, etc.).
- Strong CYP3A4 inducers (e.g., rifampin, avasimibe, 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 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. LATUDA is not approved for the treatment of patients with dementia-related psychosis.

Suicidal Thoughts and Behaviors in Pediatric and Young Adult Patients
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. Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. If NMS is suspected, immediately discontinue LATUDA and provide intensive symptomatic treatment and monitoring.

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 or may even arise after discontinuation of treatment.

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.

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.

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 healthcare provider. Consider changing the therapeutic regimen, including possibly discontinuing LATUDA, in patients whose depression is persistently worse, or who are experiencing emergent 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.

LATUDA Brief Summary - 1
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 hyperglycemia-related adverse events in patients treated with the atypical antipsychotics.

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</th>
<th>LATUDA 20 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>Mean Change from Baseline (mg/dL)</td>
<td>n=680</td>
<td>n=71</td>
<td>n=478</td>
<td>n=508</td>
<td>n=268</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>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td>8.3% (52/628)</td>
<td>11.7% (7/60)</td>
<td>12.7% (5/449)</td>
<td>6.8% (32/472)</td>
<td>10.0% (26/260)</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 mg/dL for placebo (n=95), +0.1 mg/dL for 40 mg/day (n=90), and +1.8 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

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</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=148</td>
<td>n=140</td>
<td>n=143</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>+1.8</td>
<td>-0.8</td>
<td>+1.8</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td>4.3% (6/141)</td>
<td>2.2% (3/138)</td>
<td>6.4% (9/141)</td>
</tr>
</tbody>
</table>

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=128).

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>Mean Change from Baseline (mg/dL)</td>
<td>n=302</td>
<td>n=319</td>
</tr>
<tr>
<td>Serum Glucose</td>
<td>-0.9</td>
<td>+1.2</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts to ≥ 126 mg/dL</td>
<td>1.0% (25/250)</td>
<td>1.3% (3/236)</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).

Pediatric Patients (10 to 17 years)

In studies of pediatric patients 10 to 17 years and adults with bipolar depression, changes in fasting glucose were similar. In the 6-week, placebo-controlled study of pediatric patients with bipolar depression, mean change in fasting glucose was +1.6 mg/dL for LATUDA 20 to 80 mg/day (n=145) and -0.5 mg/dL for placebo (n=145).

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: Change in Fasting Lipids in Adult Schizophrenia Studies.

Table 5: Change in Fasting Lipids in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 20 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>Mean Change from Baseline (mg/dL)</td>
<td>n=680</td>
<td>n=71</td>
<td>n=466</td>
<td>n=499</td>
<td>n=268</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>-5.8</td>
<td>-12.3</td>
<td>-5.7</td>
<td>-6.2</td>
<td>-3.5</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-13.4</td>
<td>-29.1</td>
<td>-5.1</td>
<td>-13.0</td>
<td>-3.1</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td>5.3% (30/571)</td>
<td>13.8% (8/58)</td>
<td>6.2% (5/402)</td>
<td>5.3% (23/434)</td>
<td>3.8% (9/238)</td>
</tr>
<tr>
<td>Total Cholesterol</td>
<td>≥ 240 mg/dL</td>
<td>5.3% (30/571)</td>
<td>13.8% (8/58)</td>
<td>6.2% (5/402)</td>
<td>5.3% (23/434)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>≥ 200 mg/dL</td>
<td>10.1% (53/526)</td>
<td>14.3% (7/49)</td>
<td>10.8% (41/379)</td>
<td>6.3% (25/400)</td>
</tr>
<tr>
<td>Proportion of Patients with Shifts</td>
<td>4.0% (4/101)</td>
<td>4.0% (4/101)</td>
<td>4.0% (4/101)</td>
<td>4.0% (4/101)</td>
<td>4.0% (4/101)</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=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.

Adolescents

In the adolescent short-term, placebo-controlled study, fasting serum cholesterol mean values were -9.6 mg/dL for placebo (n=95), -4.4 mg/dL for 40 mg/day (n=89), and +1.6 mg/dL for 80 mg/day (n=90), and fasting serum triglyceride mean values were +0.1 mg/dL for placebo (n=95), -0.6 mg/dL for 40 mg/day (n=89), and +8.5 mg/dL for 80 mg/day (n=92).

Bipolar Depression

Adults

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>Placeo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=303</td>
<td>n=321</td>
<td>n=310</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.04</td>
<td>+0.56</td>
<td>+0.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.02</td>
<td>+0.3</td>
<td>+0.7</td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts

<table>
<thead>
<tr>
<th></th>
<th>Placeo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>5/113</td>
<td>15/263</td>
<td>15/276</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>8/213</td>
<td>10/243</td>
<td>10/260</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 mg/dL (n=130) and -1.0 mg/dL (n=130) at week 24, respectively.

Table 7: Change in Fasting Lipids in the Adult Adjunctive Therapy Bipolar Depression Studies

<table>
<thead>
<tr>
<th></th>
<th>Placeo</th>
<th>LATUDA 20 to 60 mg/day</th>
<th>LATUDA 80 to 120 mg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change from Baseline (mg/dL)</td>
<td>n=151</td>
<td>n=143</td>
<td>n=147</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>-0.04</td>
<td>+0.56</td>
<td>+0.02</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>-0.02</td>
<td>+0.3</td>
<td>+0.7</td>
</tr>
</tbody>
</table>

Proportion of Patients with Shifts

<table>
<thead>
<tr>
<th></th>
<th>Placeo</th>
<th>LATUDA 20 to 60 mg/day</th>
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<td>5/113</td>
<td>15/263</td>
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</tr>
<tr>
<td>Triglycerides</td>
<td>8/213</td>
<td>10/243</td>
<td>10/260</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 total cholesterol and triglycerides of -0.9 (n=89) and -0.02 (n=58) mg/dL at week 24, respectively.

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, mean change in fasting cholesterol was -6.3 mg/dL for LATUDA 20 to 80 mg/day (n=144) and -1.4 mg/dL for placebo (n=145), and mean change in fasting triglyceride was -7.6 mg/dL for LATUDA 20 to 80 mg/day (n=144) and 5.9 mg/dL for placebo (n=145).

Weight Gain

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

Schizophrenia

Adulpts

Pooled data from short-term, placebo-controlled schizophrenia studies are presented in Table 8. The mean weight gain was +0.43 kg for LATUDA-treated patients compared to +0.22 kg for placebo-treated patients. Change in weight from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5 from baseline for olanzapine was +4.15 kg and for quetiapine extended-release was +2.09 kg in Studies 3 and 5.

Table 8: Mean Change in Weight (kg) from Baseline in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=896)</th>
<th>LATUDA 20 to 80 mg/day (n=71)</th>
<th>LATUDA 80 mg/day (n=484)</th>
<th>LATUDA 80 mg/day (n=526)</th>
<th>LATUDA 80 mg/day (n=291)</th>
<th>LATUDA 80 mg/day (n=114)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Change</td>
<td>-0.02</td>
<td>-0.15</td>
<td>+0.22</td>
<td>+0.54</td>
<td>+0.68</td>
<td>+0.60</td>
</tr>
</tbody>
</table>

In the uncontrolled, longer-term schizophrenia studies (primarily open-label extension studies), LATUDA was associated with a mean change in weight of -0.69 kg at week 24 (n=755), -0.53 kg at week 36 (n=443) and -0.73 kg at week 52 (n=377).

Hyperprolactinemia

As with other drugs that antagonize dopamine D₂ receptors, LATUDA elevates prolactin levels.
Hyperprolactinemia may suppress hypothalamic GnRH, resulting in reduced pituitary gonadotropin secretion. This, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both female and male patients. Galactorrhea, amenorrhea, gynecomastia, and impotence have been reported with prolactin-elevating compounds. Long-standing hyperprolactinemia, when associated with hypogonadism, may lead to decreased bone density in both female and male patients. Tissue culture experiments indicate that approximately one-third of human breast cancers are prolactin-dependent in vitro, a factor of potential importance if the prescription of these drugs is considered in a patient with previously detected breast cancer. As is common with compounds which increase prolactin release, an increase in mammary gland neoplasia was observed in a carcinogenicity study conducted with lurasidone in rats and mice. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans, but the available evidence is too limited to be conclusive.

Schizophrenia

Adults

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 13.

Table 13: Median Change in Prolactin (ng/mL) from Baseline in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>20 mg/ day</th>
<th>40 mg/ day</th>
<th>LATUDA 80 mg/ day</th>
<th>120 mg/ day</th>
<th>160 mg/ day</th>
</tr>
</thead>
<tbody>
<tr>
<td>All Patients</td>
<td>-1.9</td>
<td>-1.1</td>
<td>-1.4</td>
<td>-0.2</td>
<td>+3.3</td>
<td>+3.3</td>
</tr>
<tr>
<td>(n=672)</td>
<td>(n=70)</td>
<td>(n=476)</td>
<td>(n=495)</td>
<td>(n=284)</td>
<td>(n=115)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>-5.1</td>
<td>-4.0</td>
<td>-4.0</td>
<td>-0.2</td>
<td>+6.7</td>
<td>+7.1</td>
</tr>
<tr>
<td>(n=200)</td>
<td>(n=198)</td>
<td>(n=148)</td>
<td>(n=150)</td>
<td>(n=70)</td>
<td>(n=39)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>-1.3</td>
<td>-1.2</td>
<td>-0.7</td>
<td>-0.2</td>
<td>+3.1</td>
<td>+2.4</td>
</tr>
<tr>
<td>(n=472)</td>
<td>(n=51)</td>
<td>(n=327)</td>
<td>(n=345)</td>
<td>(n=214)</td>
<td>(n=79)</td>
<td></td>
</tr>
</tbody>
</table>

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

In the uncontrolled long-term schizophrenia 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=190) and -2.2 ng/mL at week 52 (n=207).

Adolescents

In the short-term, placebo-controlled adolescent schizophrenia study, the median 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 for males was +1.0 ng/mL and for females was +2.6 ng/mL. Median changes for prolactin by dose are shown in Table 14.

Table 14: Median Change in Prolactin (ng/mL) from Baseline in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>LATUDA 40 mg/day</th>
<th>LATUDA 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>(n=103)</td>
<td>(n=102)</td>
<td>(n=99)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>+0.70</td>
<td>+0.60</td>
<td>+4.40</td>
</tr>
<tr>
<td>(n=39)</td>
<td>(n=42)</td>
<td>(n=33)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>0.00</td>
<td>+0.75</td>
<td>+1.00</td>
</tr>
<tr>
<td>(n=64)</td>
<td>(n=60)</td>
<td>(n=66)</td>
<td></td>
</tr>
</tbody>
</table>

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

Bipolar Depression

Adults

Monotherapy

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 +3.1 ng/mL. Median changes for prolactin by dose range are shown in Table 15.

Table 15: Median Change in Prolactin (ng/mL) from Baseline in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th></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>All Patients</td>
<td>+0.3</td>
<td>+1.7</td>
<td>+3.5</td>
</tr>
<tr>
<td>(n=147)</td>
<td>(n=140)</td>
<td>(n=144)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>0.0</td>
<td>+1.8</td>
<td>+5.3</td>
</tr>
<tr>
<td>(n=82)</td>
<td>(n=79)</td>
<td>(n=88)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>+0.4</td>
<td>+1.2</td>
<td>+1.9</td>
</tr>
<tr>
<td>(n=65)</td>
<td>(n=62)</td>
<td>(n=56)</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.

The proportion of patients with prolactin elevations ≥5× upper limit of normal (ULN) was 0.4% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5× ULN was 0.6% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5× ULN was 0% and 0% for placebo-treated male patients.

In the uncontrolled, open-label, long-term bipolar depression study, patients who were treated with LATUDA as monotherapy in the short-term and continued in the longer-term study, had a median change in prolactin of -1.15 ng/mL at week 24 (n=130).

Adjunctive Therapy with Lithium or Valproate

The median change from baseline to endpoint in prolactin levels, in the adult short-term, flexible-dosed, placebo-controlled adjunctive therapy bipolar depression studies was +2.6 ng/mL with LATUDA 20 to 120 mg/day compared to 0.0 ng/mL with placebo-treated patients. The median change from baseline to endpoint for males was +2.4 ng/mL and for females was +3.2 ng/mL. Median changes for prolactin across the dose range are shown in Table 16.

Table 16: Median Change in Prolactin (ng/mL) from Baseline 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>All Patients</td>
<td>0.0</td>
<td>+2.8</td>
</tr>
<tr>
<td>(n=301)</td>
<td>(n=321)</td>
<td></td>
</tr>
<tr>
<td>Females</td>
<td>+0.4</td>
<td>+3.2</td>
</tr>
<tr>
<td>(n=156)</td>
<td>(n=162)</td>
<td></td>
</tr>
<tr>
<td>Males</td>
<td>-0.1</td>
<td>+2.4</td>
</tr>
<tr>
<td>(n=145)</td>
<td>(n=159)</td>
<td></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.

The proportion of patients with prolactin elevations ≥5× upper limit of normal (ULN) was 0.0% for LATUDA-treated patients and 0.0% for placebo-treated patients. The proportion of female patients with prolactin elevations ≥5× ULN was 0.0% for LATUDA-treated patients and 0% for placebo-treated female patients. The proportion of male patients with prolactin elevations ≥5× ULN was 0% and 0% for placebo-treated male patients.

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

Pediatric Patients (10 to 17 years)

In the 6-week, placebo-controlled bipolar depression study with pediatric patients 10 to 17 years, the median change from baseline to endpoint in prolactin levels for LATUDA-treated patients was +1.10 ng/mL and was +0.50 ng/mL for placebo-treated patients. For LATUDA-treated patients, the median change from baseline to endpoint for males was +1.5 ng/mL and for females was +3.1 ng/mL. Median changes for prolactin are shown in Table 17.
Pediatric Patients (10 to 17 years)
In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, somnolence was reported by 11.4% (20/175) of patients treated with LATUDA 20 to 80 mg/day compared to 5.8% (10/172) of placebo treated 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 adult 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 antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
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 neuroleptic malignant syndrome.

ADVERSE REACTIONS
The following adverse reactions are discussed in more detail in other sections of this Brief Summary:
• Increased Mortality in Elderly Patients with Dementia-Related Psychosis
• Suicidal Thoughts and Behaviors
• Cerebrovascular Adverse Reactions, Including Stroke, in Elderly Patients with Dementia-related Psychosis
• Neuroleptic Malignant Syndrome
• Tardive Dyskinesia
• Metabolic Changes
• Hyperprolactinemia
• Leukopenia, Neutropenia, and Agranulocytosis
• Orthostatic Hypotension and Syncope
• Falls
• Seizures
• Potential for Cognitive and Motor Impairment
• Body Temperature Dysregulation
• Activation of Mania/Hypomania
• Dysphagia

Neurological Adverse Reactions in Patients with Parkinson’s Disease or Dementia with Lewy Bodies
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.

Adults
The information below is derived from an integrated clinical study database for LATUDA consisting of 3799 adult patients exposed to one or more doses of LATUDA for the treatment of schizophrenia, and bipolar depression in placebo-controlled studies. This experience corresponds with a total experience of 1250.9 patient-years. A total of 1106 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.

Table 18: Adverse Reactions in 2% or More of LATUDA-Treated Patients in Adult Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=708)</th>
<th>LATUDA 20 mg/day (N=717)</th>
<th>LATUDA 40 mg/day (N=467)</th>
<th>LATUDA 80 mg/day (N=538)</th>
<th>LATUDA 120 mg/day (N=391)</th>
<th>LATUDA 160 mg/day (N=121)</th>
<th>All LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients Reporting Reaction</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders
Nausea 5 11 10 9 13 7 10
Vomiting 6 7 6 9 9 7 8
Dyspepsia 5 11 6 5 8 6 6
Salivary secretion <1 1 1 2 4 2 2

Nervous System Disorders
Somnolence* 7 15 16 15 26 8 17
Dizziness 2 6 4 4 5 6 4

Psychiatric Disorders
Insomnia 8 8 10 11 9 7 10
Agitation 4 10 7 3 6 5 5
Anxiety 4 3 6 4 7 3 5
Restlessness 1 1 3 1 3 2 2

Note: Figures rounded to the nearest integer

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

** Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, pschomotor retardation, tongue spasm, torticollis, tremor, and trismus.

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 80 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 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=831).

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, extrapyramidal symptoms, and nausea.

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 18.

The following are findings based on the short-term, placebo-controlled premelting premarketing adult 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, extrapyramidal symptoms, and nausea.

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.

Table 18: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in Adult Short-term Schizophrenia Studies

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=708)</th>
<th>LATUDA 20 mg/day (N=717)</th>
<th>LATUDA 40 mg/day (N=467)</th>
<th>LATUDA 80 mg/day (N=538)</th>
<th>LATUDA 120 mg/day (N=391)</th>
<th>LATUDA 160 mg/day (N=121)</th>
<th>All LATUDA (N=1508)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients Reporting Reaction</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
<td>(%)(%)</td>
</tr>
</tbody>
</table>

Gastrointestinal Disorders
Nausea 5 11 10 9 13 7 10
Vomiting 6 7 6 9 9 7 8
Dyspepsia 5 11 6 5 8 6 6
Salivary secretion <1 1 1 2 4 2 2

Nervous System Disorders
Somnolence* 7 15 16 15 26 8 17
Dizziness 2 6 4 4 5 6 4

Psychiatric Disorders
Insomnia 8 8 10 11 9 7 10
Agitation 4 10 7 3 6 5 5
Anxiety 4 3 6 4 7 3 5
Restlessness 1 1 3 1 3 2 2

Note: Figures rounded to the nearest integer

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

** Extrapyramidal symptoms include adverse event terms: bradykinesia, cogwheel rigidity, drooling, dystonia, extrapyramidal disorder, hypokinesia, muscle rigidity, oculogyric crisis, oromandibular dystonia, parkinsonism, psychomotor retardation, tongue spasm, torticollis, tremor, and trismus.
Pediatric Patients (10 to 17 years)

**Bipolar Depression**

The following findings are based on the 6-week, placebo-controlled study for bipolar depression in pediatric patients 10 to 17 years in which LATUDA was administered at daily doses ranging from 20 to 80 mg (N=175).

**Commonly Observed Adverse Reactions:** The most common adverse reactions (incidence ≥5%, and at least twice the rate of placebo) in pediatric patients (10 to 17 years) treated with LATUDA were nausea, weight increase, and insomnia.

**Adverse Reactions Associated with Discontinuation of Treatment:**

The incidence of discontinuation due to adverse reactions between LATUDA- and placebo-treated pediatric patients 10 to 17 years was 2% and 2%, respectively.

**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 pediatric patients with bipolar depression) are shown in Table 22.

### Table 22: Adverse Reactions in 2% or More of LATUDA-Treated Patients and That Occurred at Greater Incidence than in the Placebo-Treated Patients in the 6-Week Bipolar Depression Study in Pediatric Patients (10 to 17 years)

<table>
<thead>
<tr>
<th>Body System or Organ Class</th>
<th>Placebo (N=172)</th>
<th>LATUDA 20 to 80 mg/day (N=175)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastrointestinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>6</td>
<td>16</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Abdominal Pain Upper</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Investigations</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight Increased</td>
<td>2</td>
<td>7</td>
</tr>
<tr>
<td>Metabolism and Nutrition Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased Appetite</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Nervous System Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence*</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Extrapyramidal symptoms**</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Dizziness</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Psychiatric Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Abnormal Dreams</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Respiratory, Thoracic and Mediastinal Disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oropharyngeal Pain</td>
<td>2</td>
<td>2</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

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

** Extrapyramidal Symptoms **

**Schizophrenia**

### Table 23: Incidence of EPS Compared to Placebo in Adult Schizophrenia Studies

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=708) (%)</th>
<th>20 mg/day (N=71) (%)</th>
<th>40 mg/day (N=487) (%)</th>
<th>LATUDA 80 mg/day (N=538) (%)</th>
<th>120 mg/day (N=291) (%)</th>
<th>160 mg/day (N=121) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>9</td>
<td>10</td>
<td>21</td>
<td>23</td>
<td>38</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td></td>
<td>6</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>22</td>
</tr>
<tr>
<td>Akathisia</td>
<td>3</td>
<td>6</td>
<td>11</td>
<td>12</td>
<td>12</td>
<td>22</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>3</td>
<td>1</td>
<td>3</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, extra-pyramidal disorder, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.

### Table 24: 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>LATUDA 40 mg/day (N=110) (%)</th>
<th>LATUDA 80 mg/day (N=104) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td></td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>&lt;1</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>&lt;1</td>
<td>&lt;1</td>
<td>1</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

Note: Figures rounded to the nearest integer

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

** Parkinsonism includes adverse event terms: bradykinesia, drooling, extrapyramidal disorder, globellar reflex abnormal, hypokinesia, parkinsonism, and psychomotor retardation.

**Bipolar Depression Adults**

### Monotherapy

In the adult short-term, placebo-controlled monotherapy bipolar depression study, for LATUDA-treated patients, the incidence of reported events related to EPS, excluding akathisia and restlessness was 6.9% and 2.4% for placebo-treated patients. The incidence of akathisia for LATUDA-treated patients was 9.4% and 2.4% for placebo-treated patients. Incidence of EPS by dose is provided in Table 25.

### Table 25: Incidence of EPS Compared to Placebo in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Adverse Event Term</th>
<th>Placebo (N=168) (%)</th>
<th>LATUDA 80 to 120 mg/day (N=167) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All EPS events</td>
<td>5</td>
<td>12</td>
</tr>
<tr>
<td>All EPS events, excluding Akathisia/Restlessness</td>
<td></td>
<td>2</td>
</tr>
<tr>
<td>Akathisia</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Dystonia*</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Parkinsonism**</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>Restlessness</td>
<td>&lt;1</td>
<td>0</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, globellar reflex abnormal, hypokinesia, muscle rigidity, parkinsonism, psychomotor retardation, and tremor.
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 19 or those that appear elsewhere in the LATUDA label are not included.

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, 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
Clinical Laboratory Changes
Schizophrenia
Adults

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 28).

Table 28: Serum Creatinine Shifts from Normal to Baseline to High at Study End-Point in the Adult Schizophrenia Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=708)</th>
<th>LATUDA 20 mg/day (N=71)</th>
<th>LATUDA 40 mg/day (N=487)</th>
<th>LATUDA 80 mg/day (N=538)</th>
<th>LATUDA 120 mg/day (N=291)</th>
<th>LATUDA 160 mg/day (N=121)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2%</td>
<td>1%</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>7%</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 29).

Table 29: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adolescent Schizophrenia Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=103)</th>
<th>LATUDA 40 mg/day (N=97)</th>
<th>LATUDA 80 mg/day (N=97)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>2.9%</td>
<td>7.2%</td>
<td>7.2%</td>
</tr>
</tbody>
</table>

Bipolar Depression

Adults

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% (1/162) on placebo (Table 30).

Table 30: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Monotherapy Bipolar Depression Study

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=128)</th>
<th>LATUDA 20 mg/day (N=104)</th>
<th>LATUDA 80 mg/day (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>&lt;1%</td>
<td>2%</td>
<td>4%</td>
</tr>
</tbody>
</table>

Adjunctive Therapy with Lithium or Valproate

Serum Creatinine: In adult short-term, placebo-controlled premarketing adjunctive 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 31).

Table 31: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Adult Adjunctive Therapy Bipolar Depression Studies

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

Pediatric Patients (10 to 17 years)

Serum Creatinine: In the 6-week, placebo-controlled bipolar depression study in pediatric patients 10 to 17 years, the mean change from Baseline in serum creatinine was +0.021 mg/dL for LATUDA-treated patients compared to +0.009 mg/dL for placebo-treated patients. A creatinine shift from normal to high (based on the centralized laboratory definition) occurred in 6.7% (11/163) of LATUDA-treated patients and 4.5% (7/155) on placebo (Table 32).

Table 32: Serum Creatinine Shifts from Normal at Baseline to High at Study End-Point in the Bipolar Depression Study in Pediatric Patients (10 to 17 years)

<table>
<thead>
<tr>
<th>Laboratory Parameter</th>
<th>Placebo (N=155)</th>
<th>LATUDA 20 mg/day (N=163)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum Creatinine Elevated</td>
<td>4.5%</td>
<td>6.7%</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, dyspnea, and rash.

Metabolism and Nutrition Disorders: Hyponatremia.
Pregnant rats were treated with oral lurasidone at doses of 0.1, 0.5, and 50 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 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/day based on mg/m².

Pregnant rats were treated with oral lurasidone at doses of 0.4, 2, and 10 mg/kg/day during the periods of organogenesis and lactation. These doses are 0.02, 0.1 and 0.6 times the MRHD of 160 mg/day based on mg/m². No pre- and postnatal developmental effects were observed up to 0.6 times the MRHD of 160 mg/day, 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.

**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. The safety and effectiveness of LATUDA has not been established in pediatric patients less than 13 years of age with schizophrenia.

**Bipolar Depression**

The safety and effectiveness of LATUDA 20 to 80 mg/day for the treatment of bipolar depression in pediatric patients (10 to 17 years) was established in a 6-week, placebo-controlled clinical study in 347 pediatric patients. The safety and effectiveness of LATUDA has not been established in pediatric patients less than 10 years of age with bipolar 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 ages 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 serum 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 and mammary gland hyperplasia, increased vaginal mucification, and increased ovarian atrophic follicles at doses as low as 0.2 times the 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

**OVERDOSAGE**

**Human Experience**
In premarketing clinical studies, 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.

**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.

**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).
Part II: test-retest reliability of selected categorical diagnoses.


Not Bipolar, But Not Unipolar Either: Case #1


