Overview of Bipolar I Disorder in Pediatric Patients

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Overview of Bipolar I Disorder in Pediatric Patients

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Part 1: Diagnosis

- What is Bipolar I Disorder?
- *DSM-5*
- Making the Diagnosis

Part 2: Impact

- Prevalence
- Burden of Illness

Part 3: Pharmacotherapy

- Aripiprazole
- Asenapine
- Lithium carbonate
- Olanzapine
- Olanzapine/ fluoxetine
- Quetiapine fumarate
- Risperidone

Part 4: LATUDA

- Clinical Data

Learning Objectives

Upon completion of this module, you will be able to:

- Cite the diagnostic criteria for bipolar I disorder
- Describe how bipolar I disorder is diagnosed in pediatric patients
- Know the prevalence of bipolar I disorder among pediatric patients
- Describe the impact bipolar I disorder has on pediatric patients and their families
- Identify the approved treatment options for pediatric patients with bipolar I disorder
- Explain the efficacy and safety data for the use of LATUDA® (lurasidone HCl) in pediatric patients (10 to 17 years) with bipolar depression

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Different Forms of Bipolar Disorder

Bipolar I disorder

- Occurrence of ≥1 manic episode
- May be preceded by or followed by hypomanic or major depressive episodes

Manic episode

Abnormally and persistently elevated, expansive, or irritable moods lasting ≥1 week that cause significant impairment in the social or occupational functioning of the patient

Bipolar II disorder

- Occurrence of ≥1 hypomanic episode and ≥1 major depressive episode
- No history of a manic episode

Hypomanic episode

Similar to manic episode, except duration is shorter (≥4 consecutive days) and episode is not severe enough to significantly impair the patient's social or occupational functioning, or require hospitalization

The occurrence of the manic and major depressive episode(s) is not better explained by schizoaffective disorder, schizophrenia, schizophreniform disorder, delusional disorder, or other specified or unspecified schizophrenia spectrum or other psychotic disorder.

DSM-5: Manic Episode

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

   1. Inflated self-esteem or grandiosity.
   2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
   3. More talkative than usual or pressure to keep talking.
   4. Flight of ideas or subjective experience that thoughts are racing.
   5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
   6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
   7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

DSM-5: Manic Episodes in Children

The *DSM-5* should be referenced for additional guidance in diagnosing bipolar I disorder in patients younger than18 years of age.

> *In children, happiness, silliness and "goofiness" are normal in the context of special occasions; however, if these symptoms are recurrent, inappropriate to the context, and beyond what is expected for the developmental level of the child, they may meet Criterion A. If the happiness is unusual for a child (i.e., distinct from baseline), and the mood change occurs at the same time as symptoms that meet Criterion B for mania, diagnostic certainty is increased; however, the mood change must be accompanied by persistently increased activity or energy levels that are obvious to those who know the child well.*

Special considerations are necessary to detect the diagnosis in children. The quote above is an example from *DSM-5* of additional guidance in diagnosing bipolar I disorder in patients younger than 18 years of age.

DSM-5: Major Depressive Episode

Major depressive episodes are common in bipolar I disorder, but are not required for the diagnosis of bipolar I disorder.

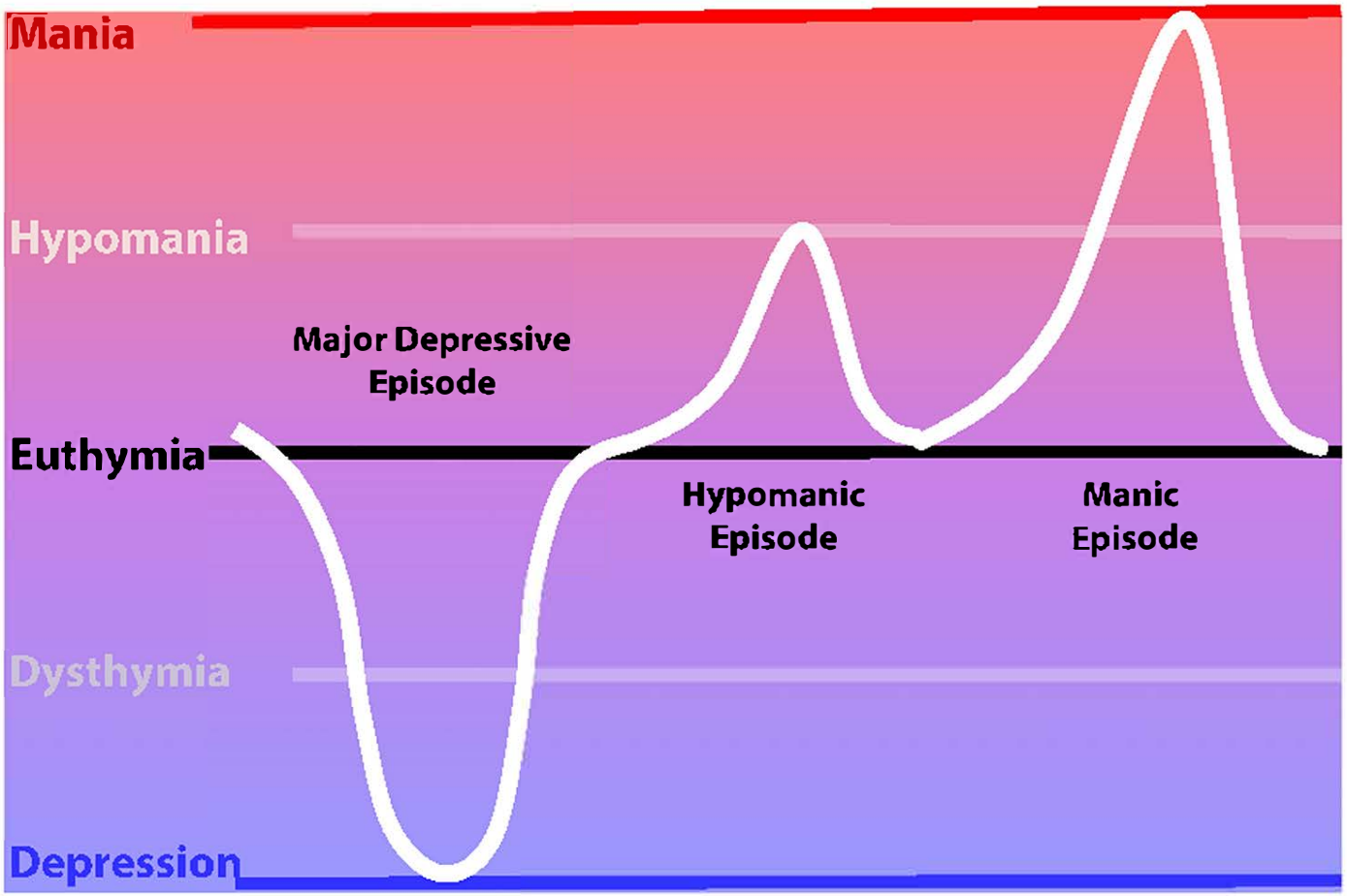
A. Five (or more) of the following symptoms have been present during the same 2-week period and represent a change from previous functioning; at least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure.
Note: Do not include symptoms that are clearly attributable to another medical condition.

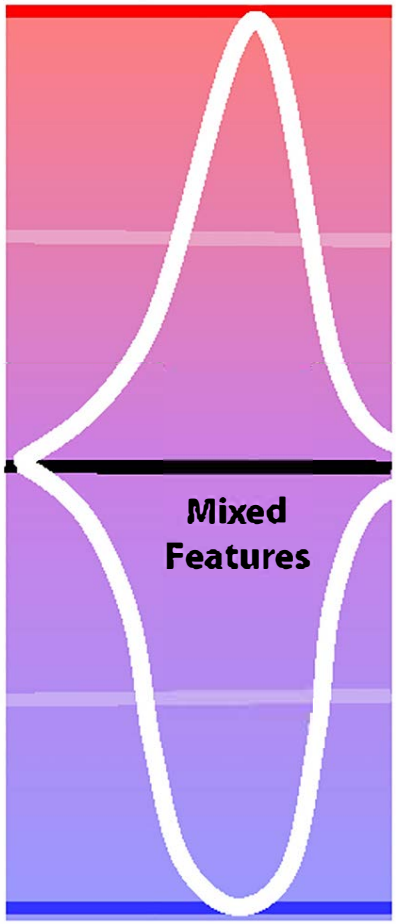
1. Depressed mood most of the day, nearly every day, as indicated by either subjective report (e.g., feels sad, empty, or hopeless) or observation made by others (e.g., appears tearful). (**Note:** In children and adolescents, can be irritable mood.)
2. Markedly diminished interest or pleasure in all, or almost all, activities most of the day, nearly every day (as indicated by either subjective account or observation).
3. Significant weight loss when not dieting or weight gain (e.g., a change of more than 5% of body weight in a month), or decrease or increase in appetite nearly everyday. (**Note:** In children, consider failure to make expected weight gain.)
4. Insomnia or hypersomnia nearly every day.
5. Psychomotor agitation or retardation nearly every day (observable by others; not merely subjective feelings of restlessness or being slowed down).
6. Fatigue or loss of energy nearly every day.
7. Feelings of worthlessness or excessive or inappropriate guilt (which may be delusional) nearly every day (not merely self-reproach or guilt about being sick).
8. Diminished ability to think or concentrate, or indecisiveness, nearly every day (either by subjective account or as observed by others).
9. Recurrent thoughts of death (not just fear of dying), recurrent suicidal ideation without a specific plan, or a suicide attempt or a specific plan for committing suicide.

B. The symptoms cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.

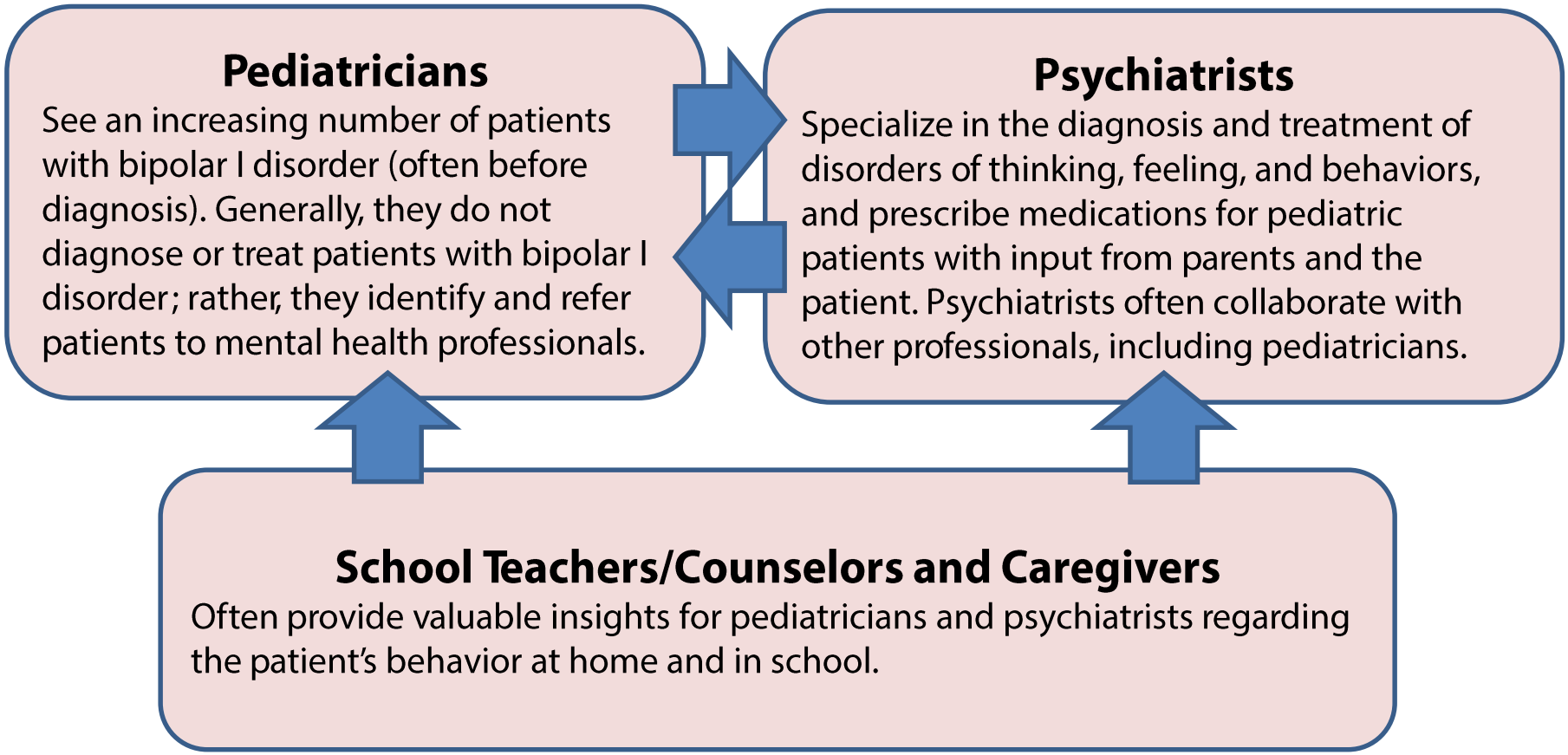
C. The episode is not attributable to the physiological effects of a substance or another medical condition.

Mood Episodes





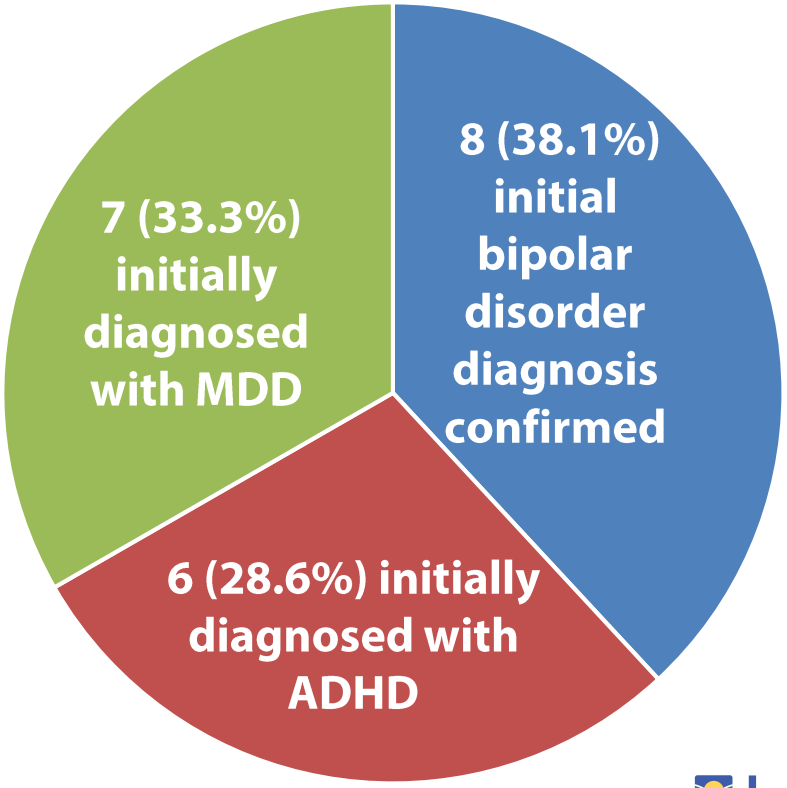
Making a Diagnosis: Roles



Making a Diagnosis: Challenges

- Bipolar I disorder in pediatric patients is often misdiagnosed as ADHD or major depressive disorder (MDD)
  - Symptoms such as irritability can be associated with either MDD or bipolar disorder
- A study of pediatric mental health patients (ages 7 to 18 years) had their diagnoses reassessed

21 Pediatric Patients
Diagnosed With Bipolar Disorder on Reassessment



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Prevalence

Adults

- The estimated yearly prevalence of bipolar I disorder, as reported by the *DSM-5*, in the United States is 0.6%
  - ~1.5 million adults over 18 years of age

Children

- A meta-analysis of 12 epidemiologic studies of psychiatric disorder prevalences involving over 16,000 patients ranging in age from 7 to 21 years old was performed
  - The overall mean prevalence rate for bipolar disorder was 1.8%
  - The mean prevalence rate for bipolar I disorder was 1.2%

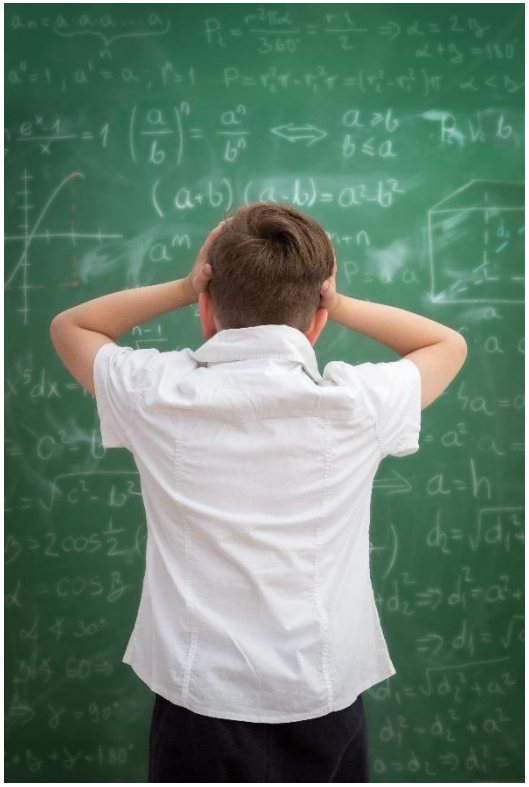
Burden of Illness: Suicide

Increased Risk of Suicide

- Early-onset bipolar I disorder may result in a worse long-term prognosis, including elevated rates of comorbid diagnosis and increased risk of suicide
- In a study of over 400 pediatric patients with bipolar disorders, more than 70% had a history of suicidal ideation
  - 35% of the patients with bipolar I disorder had attempted suicide at least once in their lifetime

Burden of Illness: Disability and Functional Impairment

- Bipolar disorder is the fourth leading cause of disability among children and young adults (ages 10 to 24) throughout the world
- It may be associated with compromised academic functioning
  - ~45% of patients have reading difficulties
  - ~30% have math difficulties
  - ~67% require special education services



Burden of Illness: Caregivers

- Taking care of a child with bipolar disorder can be very difficult for parents, family, and other caregivers
- Stress for caregivers can result in:
  - Neglecting their own health
  - Missing work
  - Losing free time
  - Strained interpersonal relationships
  - Physical and mental exhaustion
- Increased stress on caregivers can have negative consequences for the patient
  - Patients with families who report higher stress are less adherent to medications and are more likely to have a major mood episode over time

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Pharmacologic Treatment

Agent(s)	Bipolar I Disorder Indication for Pediatric Patients
Aripiprazole (Abilify®)	• Acute treatment of manic and mixed episodes associated with bipolar I disorder, as monotherapy or as adjunct to lithium or valproate • For patients ≥10 years of age
Asenapine (Saphris®)	• Acute monotherapy of manic or mixed episodes • For patients ≥10 years of age
Lithium carbonate	• Treatment of manic episodes of bipolar disorder • Maintenance treatment for individuals with a diagnosis of bipolar disorder • Not recommended for children <12 years old
Olanzapine (Zyprexa®)	• Acute treatment of manic or mixed episodes associated with bipolar I disorder • For patients ≥13 years of age
Olanzapine/fluoxetine (Symbyax®)	• Treatment of acute depressive episodes associated with bipolar I disorder • For patients ≥10 years of age
Quetiapine fumarate (Seroquel®)	• Acute treatment of manic episodes associated with bipolar I disorder, both as monotherapy and as an adjunct to lithium or divalproex • For patients ≥10 years of age
Risperidone (Risperdal®)	• Treatment of acute manic or mixed episodes associated with bipolar I disorder • For patients ≥10 years of age

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Aripiprazole

Dosage and administration in pediatric patients (10 to 17 years of age)

- Monotherapy:
  - Recommended starting dose: 2 mg/day
  - Titrate to 5 mg/day after 2 days
  - Target dose of 10 mg/day after 2 additional days
- Adjunctive therapy:
  - Recommended dosing is same as monotherapy
- For both monotherapy and adjunctive therapy, subsequent dose increases, if needed, should be administered in 5-mg/day increments
- Can be given without regard to meals
- Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Aripiprazole

Efficacy

- 4-week, double-blind, placebo-controlled trial
- 296 patients (10 to 17 years of age) who met *DSM-IV* criteria for bipolar I disorder manic or mixed episodes with or without psychotic features
  - Young Mania Rating Scale (YMRS) score ≥20 at baseline
- 3 treatment groups:
  - Aripiprazole (10 mg/day)
  - Aripiprazole (30 mg/day)
  - Placebo
- Both doses of aripiprazole were superior to placebo in change from baseline to Week 4 on the YMRS total score

Safety

- 5 most common adverse reactions:
  - Somnolence
  - Extrapyramidal disorder
  - Fatigue
  - Nausea
  - Akathisia
- 7% of patients in the aripiprazole group discontinued treatment due to adverse events, compared to 2% in the placebo group

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Asenapine

Dosage and administration in pediatric patients (10 to 17 years of age)

- Recommended dose is 2.5 to 10 mg twice daily
- Dose may be adjusted for individual response and tolerability
  - Initial dose 2.5 mg twice daily
  - After 3 days, can increase dose to 5 mg twice daily
  - After additional 3 days, can increase to 10 mg twice daily
- Pediatric patients appear to be more sensitive to dystonia with initial dosing with asenapine when the recommended dose escalation schedule is not followed
- Branded only, no generic formulations currently available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Asenapine

Efficacy

- Acute treatment of mania in 403 pediatric patients (ages 10 to 17) with bipolar I disorder
- 3-week, placebo-controlled, double-blind trial
- 4 treatment groups:
  - Asenapine 2.5 mg twice daily
  - Asenapine 5 mg twice daily
  - Asenapine 10 mg twice daily
  - Placebo
- Asenapine was statistically superior to placebo in improving YMRS total score and the CGI-BP Severity of Illness overall score from baseline

Safety

- 5 most common adverse reactions:
  - Somnolence
  - Abdominal pain
  - Headache
  - Fatigue
  - Oral hypoesthesia
- Discontinuation rates:
  - Asenapine 2.5 mg twice daily: 6.7%
  - Asenapine 5 mg twice daily: 5.1%
  - Asenapine 10 mg twice daily: 5.1%
  - Placebo: 4%

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Lithium

Acute mania

- Optimal patient response:
  - Lithium carbonate: usually established and maintained with 600 mg TID
  - Lithium oral solution: usually established and maintained with 10 mL (2 full teaspoons) TID
- Dosage must be individualized according to serum levels and clinical response
- Regular monitoring of the patient's clinical state and of serum lithium levels is necessary
  - Serum levels should be determined twice per week during the acute phase, and until the serum level and the clinical condition of the patient have been stabilized

Maintenance

- Desirable serum lithium levels: 0.6 to 1.2 mEq/L
- This level usually can be maintained with:
  - 300 mg of lithium carbonate TID or QID, or
  - 5 mL (1 full teaspoon) of lithium oral solution TID or QID
- Serum lithium levels in uncomplicated cases
  - Monitored at least every 2 months

Contraindications

- Lithium should not be given to patients with significant renal disease or CVD, severe debilitation or dehydration, or sodium depletion, or to patients receiving diuretics

General precautions

- Where hypothyroidism exists, careful monitoring of thyroid function during lithium stabilization and maintenance allows for correction of changing thyroid parameters

Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Lithium

The lithium studies presented here are not the pivotal studies on which the FDA based its approval of lithium. The studies are provided for background only.

Efficacy

- 8-week, double-blind, placebo-controlled study of 81 children and adolescents (7 to 17 years old) with bipolar I disorder
- Treatment groups:
  - Lithium
  - Placebo
- Primary endpoint: change in YMRS
  - At end of study, change in YMRS was significant in favor of lithium

Safety

- The following adverse events are listed as warnings and precautions in the lithium prescribing information: lithium toxicity, lithium-induced polyuria, hyponatremia, lithium-induced chronic kidney disease, encephalopathic syndrome, serotonin syndrome, hypothyroidism or hyperthyroidism, hypercalcemia and hyperparathyroidism, unmasking of Brugada syndrome, and pseudotumor cerebri.

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Lithium

The lithium studies presented here are not the pivotal studies on which the FDA based its approval of lithium. The studies are provided for background only.

Efficacy

- 6-week, open-label, single arm study of 27 adolescents (12 to 18 years old) with bipolar depression
- Treatment group:
  - Lithium
- Primary endpoint: change from baseline in CDRS-R
  - CDRS-R scores were significantly lower relative to baseline

Safety

- Adverse events identified in the prescribing information as voluntary reports following use of lithium included the following categories, and each category had specific adverse events listed within them: central nervous system reactions, electroencephalography (EEG) changes, cardiovascular reactions, electrocardiography (ECG) changes, gastrointestinal reactions, genitourinary reactions, dermatologic reactions, autonomic nervous system reactions, and miscellaneous reactions

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Olanzapine

Dosage and administration in adolescent patients (13 to 17 years of age)

- Acute treatment of manic or mixed episodes
  - Recommended starting dose is 2.5 or 5 mg once daily
    - Target dose: 10 mg/day
    - Efficacy shown for flexible doses from 2.5 mg/day to 20 mg/day
    - Dose increments/decrements of 2.5 or 5 mg recommended
  - Administer once daily without regard to meals
- Maintenance
  - Efficacy in adolescent population not studied, but can be extrapolated from adult data
  - It is recommended that responding patients continue treatment beyond acute response at the lowest dose needed to maintain remission
    - Patients should be periodically reassessed to determine need for maintenance treatment
- Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Olanzapine

Efficacy

- Acute treatment of manic or mixed episodes in 161 adolescent patients (ages 13 to 17) with bipolar I disorder
- 3-week, double-blind, placebo-controlled, randomized trial
- 2 treatment groups:
  - Olanzapine (dosed flexibly: 2.5 to 20 mg/day)
  - Placebo
- Olanzapine demonstrated statistically significantly greater mean reduction in YMRS total score compared to placebo

Safety

- 5 most common adverse reactions:
  - Sedation
  - Weight increase
  - Headache
  - Increased appetite
  - Dizziness

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Olanzapine/fluoxetine

Dosage and administration in pediatric patients (10 to 17 years of age)

- Administer once daily in the evening without regard to meals
- Generally begin with the 3-mg/25-mg capsule with a recommended target dose within the approved dosing range:
  - 6/25 mg; 6/50 mg; 12/25 mg; 12/50 mg
- The safety of doses >12 mg of olanzapine and >50 mg of fluoxetine has not been evaluated in pediatric clinical studies
- Periodically reexamine the need for continued pharmacotherapy
- Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Olanzapine/fluoxetine

Efficacy

- 8-week, randomized, double-blind, placebo-controlled
- 255 patients (10 to 17) years of age, who met *DSM-IV-TR* criteria for bipolar I disorder, depressed
- 2 treatment groups:
  - Olanzapine/fluoxetine (dosed flexibly: 3/25 mg/day to 12/50 mg/day)
  - Placebo
- Primary outcome measure: change from baseline to Week 8 in the CDRS-R total score
- Olanzapine/fluoxetine statistically significantly superior to placebo in reduction of the CDRS-R total score

Safety

- 5 most common treatment-emergent adverse reactions for olanzapine/fluoxetine included:
  - Somnolence
  - Increased weight
  - Increased appetite
  - Tremor
  - Increased hepatic enzymes
- 14.1% of patients in the olanzapine/fluoxetine group discontinued treatment due to adverse events, compared to 5.9% in the placebo group

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Quetiapine fumarate

Dosage and administration in pediatric patients (10 to 17 years of age)

- Day 1: 25 mg twice daily
- Day 2: Twice-daily dosing totaling 100 mg
- Day 3: Twice-daily dosing totaling 200 mg
- Day 4: Twice-daily dosing totaling 300 mg
- Day 5: Twice-daily dosing totaling 400 mg
- Further adjustments should be in increments no greater than 100 mg/day within the recommended dose range of 400 to 600 mg/day
  - The maximum dose is 600 mg/day
- Based on response and tolerability, quetiapine fumarate may be administered 3 times daily
- Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Quetiapine fumarate

Efficacy

- Acute treatment of manic episodes in pediatric patients (ages 10 to 17) with bipolar I disorder
- 3-week, double-blind, placebo-controlled, multicenter trial
- 3 treatment groups:
  - Quetiapine fumarate 400 mg/day (n = 95)
  - Quetiapine fumarate 600 mg/day (n = 98)
  - Placebo (n = 91)
- Both quetiapine fumarate 400 mg/day and 600 mg/day showed superiority to placebo in the mean change from baseline in total YMRS scores

Safety

- 5 most common adverse reactions:
  - Somnolence
  - Dizziness
  - Fatigue
  - Increased appetite
  - Nausea
- 11.4% of patients receiving quetiapine fumarate discontinued treatment due to adverse reactions, compared to 4.4% receiving placebo

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Risperidone

Dosage and administration in pediatric patients (10 to 17 years of age)

- Initial dose 0.5 mg once daily (morning or evening)
  - Adjust dose ≥24 hours in increments of 0.5 mg or 1.0 mg (as tolerated)
  - Target dose 1 mg to 2.5 mg per day
- Patients experiencing somnolence may benefit from half the dose twice daily
- No data supports the use of risperidone for maintenance treatment beyond 3 weeks
  - Physicians should periodically re-evaluate long-term risks and benefits of risperidone for the individual patient
- Generic formulations available

Please see each agent's Prescribing Information for complete details

Pharmacologic Treatment: Risperidone

Efficacy

- 3-week, randomized, double-blinded, placebo-controlled trial
- Treatment of mania in 169 pediatric patients (10 to 17 years of age) with bipolar I disorder
- 3 treatment groups:
  - Risperidone 0.5 to 2.5 mg (mean dose 1.9 mg)
  - Risperidone 3 to 6 mg (mean dose 4.7 mg)
  - Placebo
- Risperidone demonstrated significant reduction in YMRS score from baseline compared to placebo
  - Doses >2.5 mg did not show greater efficacy compared to ≤2.5 mg dose

Safety

- 5 most common adverse reactions:
  - Sedation
  - Fatigue
  - Upper abdominal pain
  - Nausea
  - Dizziness
- 12% of patients in the combined risperidone treatment group discontinued treatment due to adverse events, compared to 7% in the placebo group

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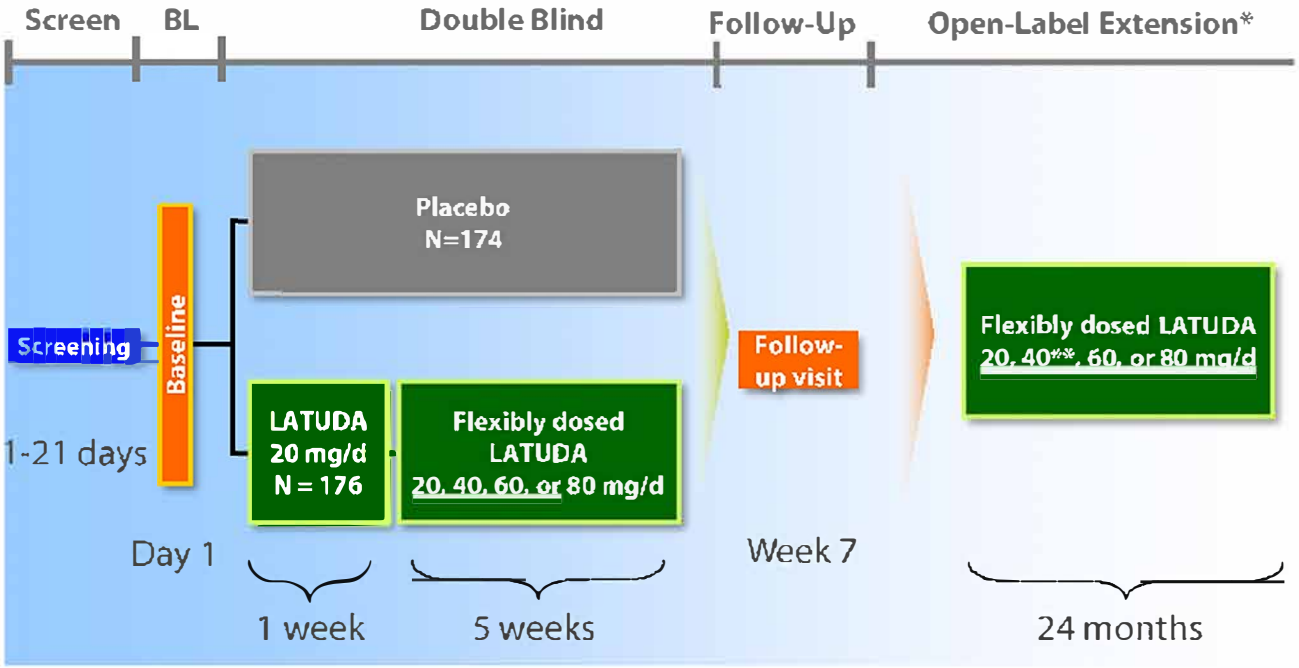
Study Design of the Pediatric Bipolar Depression Trial

A randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel-group study to evaluate the efficacy and safety of LATUDA in pediatric patients (10 to 17 years) with bipolar depression



FPI: March 2014

*Subjects who have completed all visits in the core efficacy study are eligible to enter a 104-week open-label extension study.
**All eligible subjects who enroll will be dosed with 40 mg, and flexible dosing will be permitted thereafter.

DelBello MP, Goldman R, Phillips D, et al. Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double-Blind, Placebo-Controlled Study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025.

Latuda (lurasidone HCl) tablets 20mg | 40mg | 80mg

Efficacy Measures: CDRS-R

- **Children's Depression Rating Scale-Revised (CDRS-R)**
  - 17-item clinician-rated instrument that measures severity of depression-related symptoms
  - Total score 17 to 113
    - Score ≥40 indicates depression; ≤28 indicates minimal or no symptoms (remission)

1. Impaired schoolwork (rate 1 to 6)
2. Difficulty having fun (rate 1 to 7)
3. Social withdrawal (rate 1 to 7)
4. Sleep disturbance (rate 1 to 5)
5. Appetite disturbance (rate 1 to 5)
6. Excess fatigue (rate 1 to 7)
7. Physical complaints (rate 1 to 7)
8. Irritability (rate 1 to 6)
9. Excessive guilt (rate 1 to 6)
10. Low self-esteem (rate 1 to 7)
11. Depressed feelings (rate 1 to 7)
12. Morbid ideation (rate 1 to 7)
13. Suicide ideation (rate 1 to 7)
14. Excessive weeping (rate 1 to 6)
15. Depressed facial affect (rate 1 to 7)
16. Listless speech (rate 1 to 5)
17. Hypoactivity (rate 1 to 6)

Efficacy Measures: CGI-BP-S

- **Clinical Global Impression-Bipolar Severity Assessment (CGI-BP-S)**
  - 7-point scale to assess symptoms of bipolar disorder

I. SEVERITY of Illness

Considering your total clinical experience with bipolar patients, how severely ill has the patient been during the assessment period? ACUTE ASSESSMENTS reflect the past week. PROPHYLACTIC ASSESSMENTS reflect the time on current prophylactic medication(s) with emphasis on the most recent episodes.

Normal, not ill	Minimally ill	Mildly ill	Moderately ill	Markedly ill	Severely ill	Very severely ill
1	2	3	4	5	6	7

a. Mania _____

b. Depression _____

c. Overall Bipolar Illness _____

Key Inclusion Criteria

- Male and female subjects aged 10 to 17 years old
- Bipolar I depression diagnosis based on *DSM-5* criteria
- Major depressive episode duration 1 to 12 months
- CDRS-R total score ≥45 and ≤85 at screening and baseline
- Diagnosis confirmed via the Schedule for Affective Disorders and Schizophrenia for School-age Children – Present and Lifetime (K-SADS-PL) interview administered by a trained clinician
- YMRS score ≤15 at study entry, YMRS item 1 (elevated mood) score of ≤2 at screening and baseline

- Within 3rd to 97th percentile for gender-specific BMI-for-age growth charts from the WHO

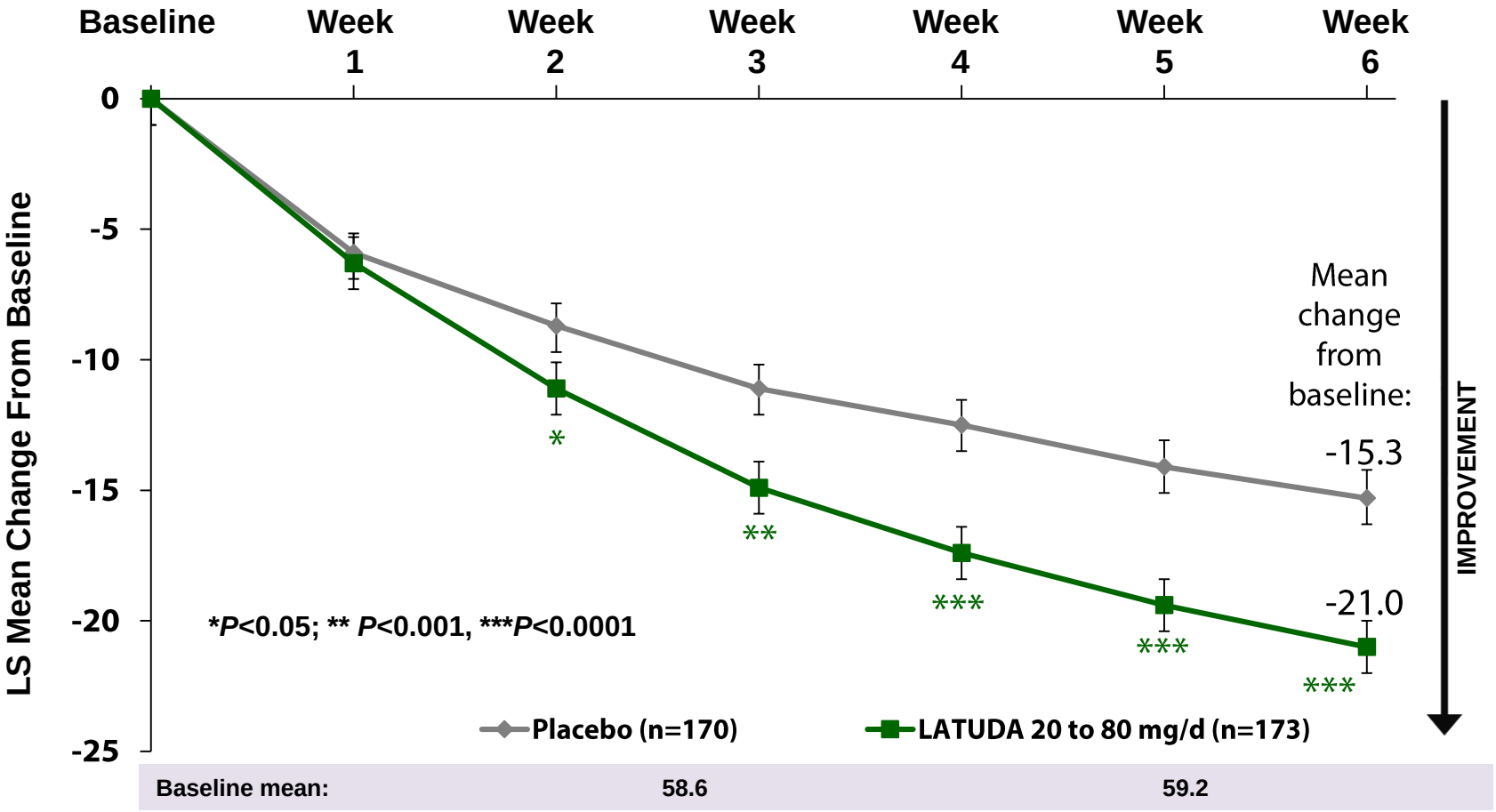
Subjects also eligible for enrollment:

- History of rapid cycling (≥4 but <8 episodes in the previous 12 months)
- Diagnosis of ADHD, if receiving a stable regimen of stimulant medication for at least 30 days before screening
- Currently being treated in an inpatient, outpatient, partial hospital, or therapeutic day program setting

Study Objectives – Efficacy

- **Primary Endpoint**
  - Change from baseline to Week 6 in the CDRS-R total score compared to placebo
- **Key Secondary Endpoint**
  - Change from baseline to Week 6 in the CGI-BP-S score (depression) compared to placebo

PRIMARY ENDPOINT - CDRS-R Total Score Change From Baseline



DelBello MP, Goldman R, Phillips D, et al. Efficacy and Safety of Lurasidone in Children and Adolescents With Bipolar I Depression: A Double-Blind, Placebo-Controlled Study. *J Am Acad Child Adolesc Psychiatry*. 2017;56(12):1015-1025.

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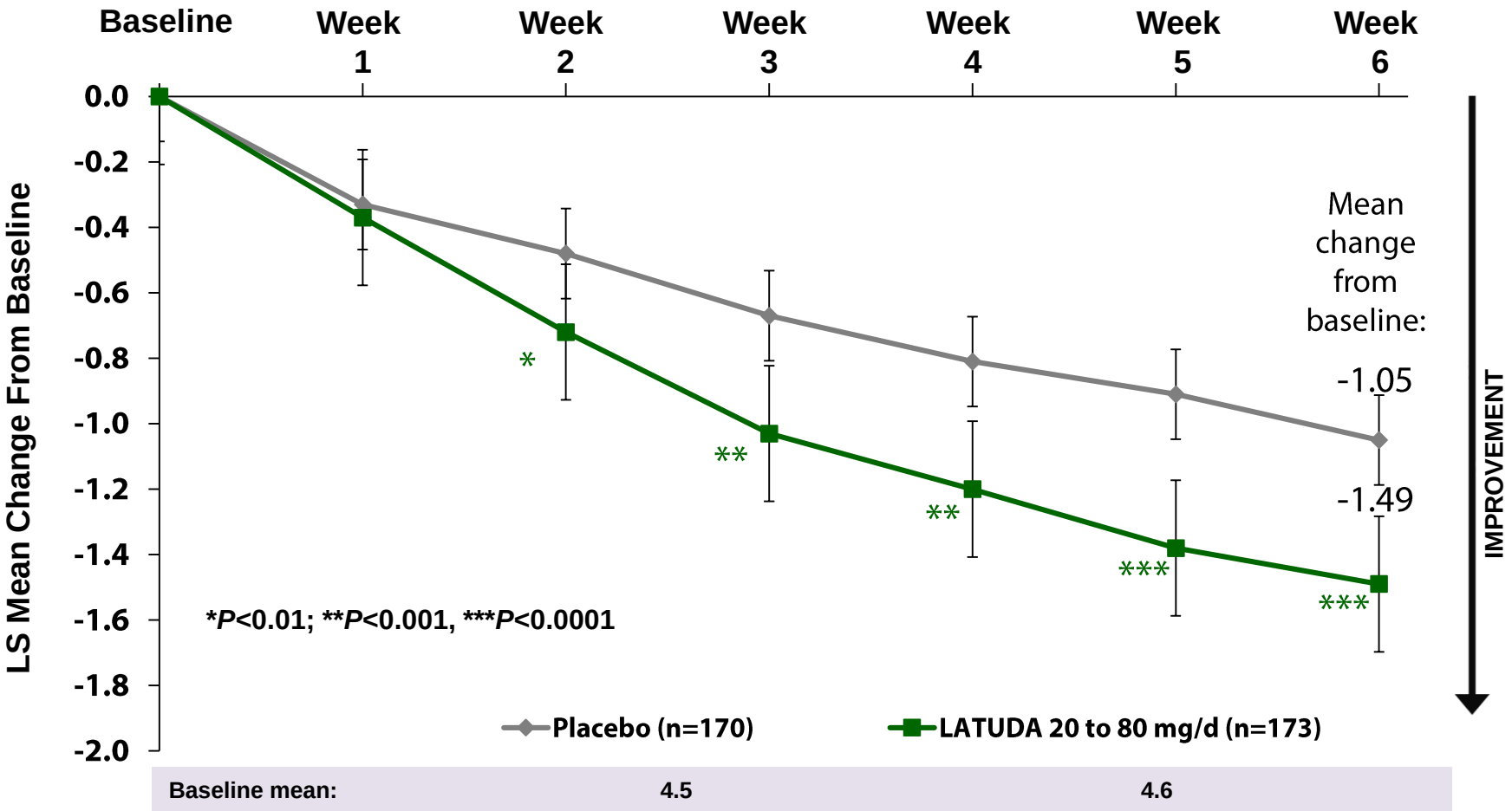
KEY SECONDARY ENDPOINT - CGI-BP-S (Depression Score) Change From Baseline



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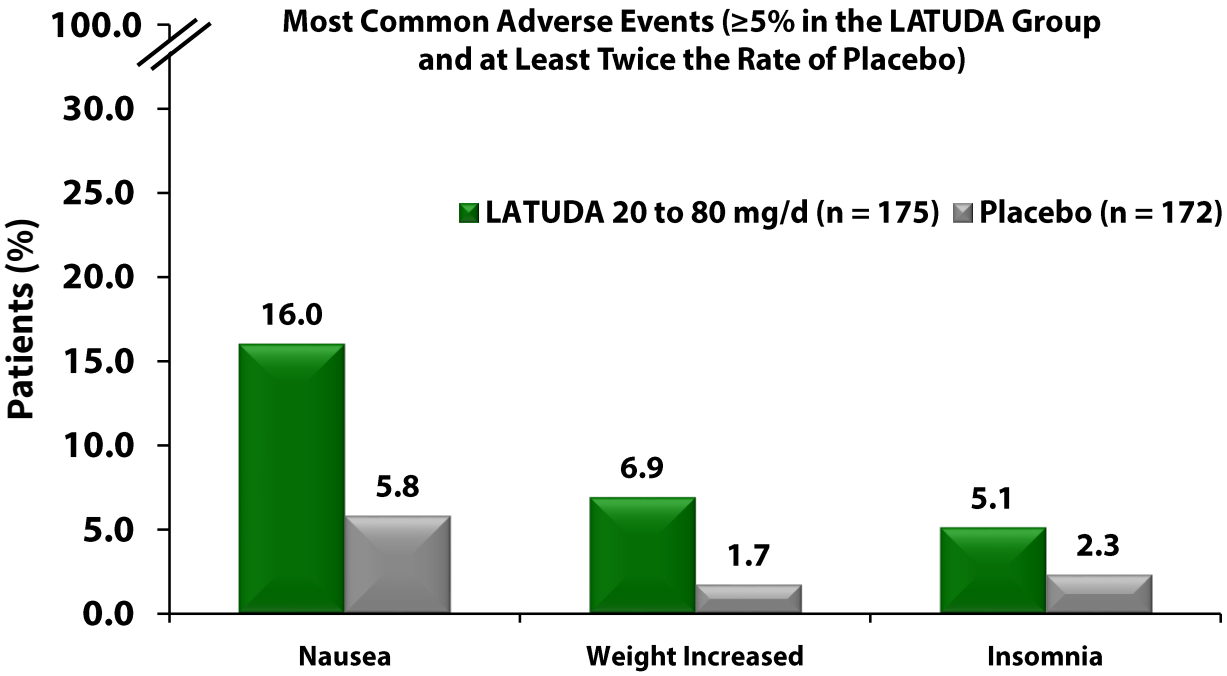
Adverse Events



- Mean weight gain similar:
  - LATUDA: +0.74 kg
  - Placebo: +0.44 kg
- No clinically meaningful differences between treatment groups in:
  - Lipid levels
  - Glucose levels
  - Prolactin levels
- No treatment-emergent adverse events related to elevated prolactin levels (galactorrhea)

No patients discontinued treatment due to these AEs.

- Placebo group: 1 patient each discontinued due to depression, mania, and psychotic disorder
- LATUDA group: 1 patient each discontinued due to fatigue, restless leg syndrome, and bipolar I disorder.

Serious AEs were experienced by 4 patients (2.3%) in placebo group and 2 patients (1.1%) in the LATUDA group.
Safety population.

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Key Takeaways

Diagnosis

- For a diagnosis of bipolar I disorder, the patient must experience at least one manic episode
  - Manic episodes are abnormally and persistently elevated, expansive, or irritable moods lasting at least a week which cause significant impairment in the social or occupational functioning of the patient
  - Criteria for a manic episodes are included in the *DSM-5* from the American Psychiatric Association
- Major depressive disorders are common in bipolar I disorder
  - 5 or more criteria from the *DSM-5* for a major depressive episode must be met
    - At least one of the symptoms is either (1) depressed mood or (2) loss of interest or pleasure
- Roles
  - Pediatricians identify patients with a reasonable suspicion of bipolar disorder and refer those patients to appropriate mental health professionals, such as a psychiatrist
  - Psychiatrists specialize in the diagnosis and treatment of disorders of thinking, feeling, and behaviors, including bipolar I disorder
  - School teachers, counselors, and caregivers provide valuable insight to psychiatrists and pediatricians regarding the patient's behavior at home and in school

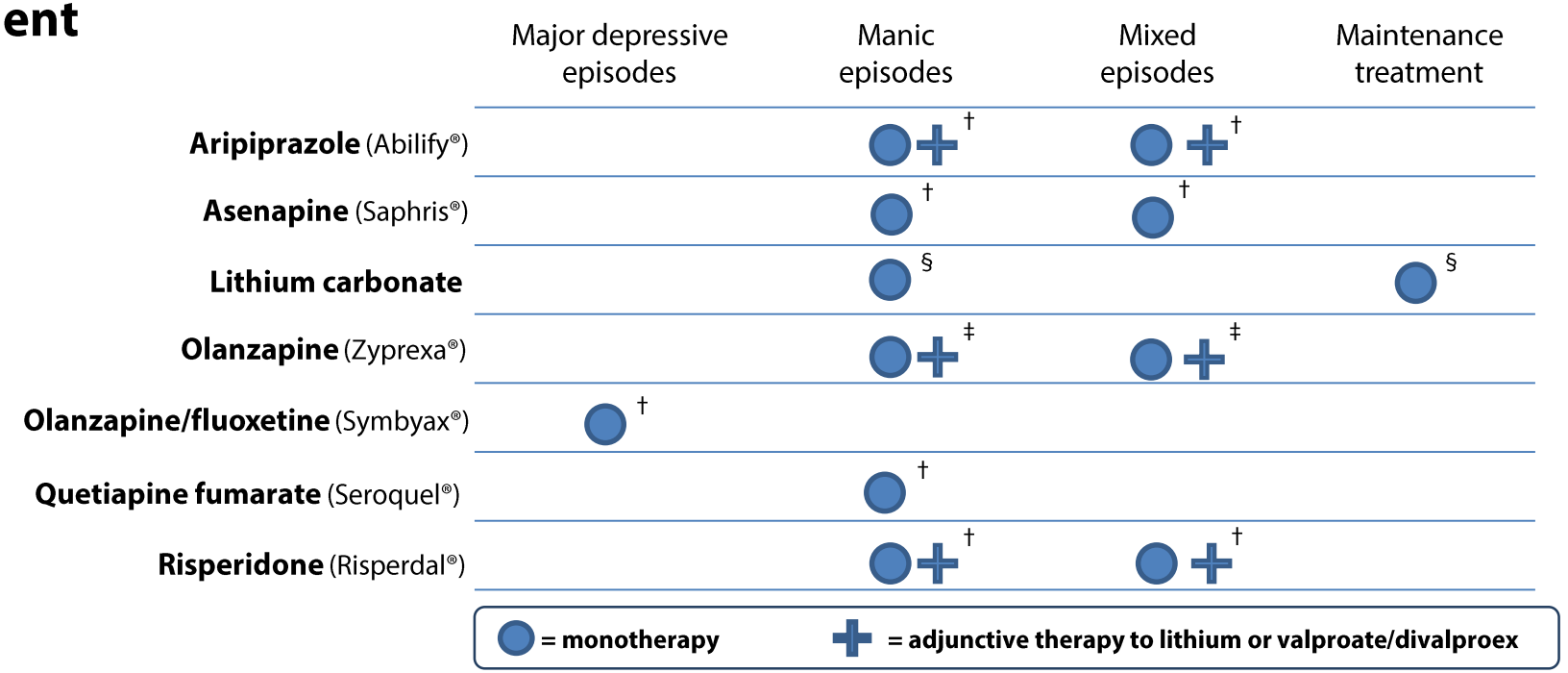
Key Takeaways (Cont'd)

Impact

- The estimated prevalence of bipolar I disorder among children and adolescents (ages 7 to 21 years old) is 1.2%
- Burdens of bipolar I disorder include:
  - Increased risk of suicide: 35% of patients with bipolar I disorder attempt suicide within their lifetime
  - Disability and functional impairment: bipolar disorder is the fourth leading cause of disability among children and young adults worldwide; bipolar disorder in pediatric patients is associated with compromised academic functioning
  - Burden on caregivers: a diagnosis of bipolar I disorder can cause stress for caregivers and families, with negative consequences for the caregivers and the patient

Key Takeaways (Cont'd)

Treatment



† Ages 10 to 17 years; ‡ Ages 13 to 17 years; § Not recommended ages <12 years at this time

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Key Takeaways (Cont'd)

LATUDA®

- Indications:
  - 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)
- A randomized, 6-week, double-blind, placebo-controlled, flexible-dose, parallel-group study evaluated the efficacy and safety of LATUDA in pediatric patients (ages 10 to 17 years) with bipolar I depression
  - Treatment:
    - LATUDA was initiated at a daily dose of 20 mg for 7 days, with flexible dosing in the range of 20 to 80 mg/day permitted after 7 days
    - Placebo
  - The primary efficacy endpoint was mean change from baseline to Week 6 in the CDRS-R total score compared to placebo
    - The mean change from baseline to Week 6 on the CDRS-R total score was significantly greater in the LATUDA group compared with the placebo group (-21.0 vs -15.3; $P<0.0001$)
  - The key secondary endpoint was mean change from baseline to Week 6 in the CGI-BP-S score for depression compared to placebo
    - The mean change from baseline to Week 6 on the CGI-BP-S depression severity score was significantly greater in the LATUDA group compared with the placebo group (-1.49 vs -1.05; $P<0.0001$)
  - Commonly observed adverse reactions (incidence ≥5% and at least twice the rate for placebo) were: nausea, weight increase, and insomnia.

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