A Focus on

BIPOLAR DEPRESSION

Overcoming Diagnostic Barriers and Optimizing Long-term Patient Outcomes

FACULTY

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President & Medical Director, Comprehensive Primary Care
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Memphis, Tennessee

LEARNING OBJECTIVES

Upon completion of the following activity, participants should be better able to:

1. Discuss clinically relevant pathophysiology of bipolar disorder, including epidemiologic and mechanistic relationships with cardiometabolic disturbances
2. Identify patients with bipolar depression based on comprehensive patient histories, risk factors, key presenting symptoms, and the latest diagnostic criteria
3. Tailor therapeutic regimens for bipolar depression to reflect efficacy, safety, and tolerability of approved agents and common patient comorbidities
4. Engage patients with bipolar depression to motivate active participation in ongoing care and improve treatment adherence

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Jim Kappler, PhD has nothing to disclose.

CLINICAL RESOURCE CENTER

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A FOCUS ON BIPOLAR DEPRESSION

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9:15 – 10:30am

A Focus on Bipolar Depression:
Overcoming Diagnostic Barriers and Optimizing Long-Term Patient Outcomes

SPEAKERS
Joseph Calabrese, MD
William Jackson, MD

Educational Objectives

• Discuss clinically relevant pathophysiology of bipolar disorder, including epidemiologic and mechanistic relationships with cardiometabolic disturbances
• Identify patients with bipolar depression based on comprehensive patient histories, risk factors, key presenting symptoms, and the latest diagnostic criteria
• Tailor therapeutic regimens for bipolar depression to reflect efficacy, safety, and tolerability of approved agents and common patient comorbidities
• Engage patients with bipolar depression to motivate active participation in ongoing care and improve treatment adherence

Medications Discussed in Program

• Medication classes
  – Tricyclic antidepressants
  – SNRIs
  – SSRIs
  – Atypical antipsychotics

• Specific medications
  – Venlafaxine
  – Bupropion
  – Sertraline
  – Olanzapine
  – Olanzapine/fluoxetine
  – Quetiapine
  – Lurasidone
  – Lithium
  – Valproate (divalproex sodium)
  – Lamotrigine
  – Carbamazepine

Presenter Disclosure Information

The following relationships exist related to this presentation:


Off-Label/Investigational Discussion

► In accordance with pmICME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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Bipolar disorder linked to aberrant connections and activity in limbic and cortical regions that process emotion. Disrupted emotional homeostasis and increased risks of extreme mood states.

Patients show altered signaling in circuits mediated by monoamines, glutamate, and GABA. Changes associated with impulsivity, psychomotor dysregulation, suicidality, and depression, among other clinical symptoms.

Clinical profiles of medications determined by affinities for and effects on various receptor subtypes.

- 5-HT1A agonism and 5-HT2A and dopaminergic antagonism lead to antidepressive and mood-stabilizing effects.
- Antagonism of histaminergic H1 and muscarinic M1 and M3 receptors increases risk of weight gain, other metabolic disturbances, and sedation.

### Scientific Insights Into Bipolar Disorder

**Key Points**

- Bipolar disorder linked to aberrant connections and activity in limbic and cortical regions that process emotion.
- Disrupted emotional homeostasis and increased risks of extreme mood states.
- Patients show altered signaling in circuits mediated by monoamines, glutamate, and GABA. Changes associated with impulsivity, psychomotor dysregulation, suicidality, and depression, among other clinical symptoms.
- Clinical profiles of medications determined by affinities for and effects on various receptor subtypes.

### Burdens of Bipolar Depression

**Key Points**

- Affective episodes cause neurotoxicity and neural degeneration in the brain.
- Decreased BDNF levels and increased oxidative stress.
- High risk of suicide.
- Suicidal ideation and attempts predominantly linked to depressive phase.
- More depressive episodes associated with cognitive issues, risks for late-life dementia, higher rates of medical and psychological comorbidities.

### Multiple Mood Episodes in Bipolar Disorder

**Relapse Risk and Treatment Resistance**

<table>
<thead>
<tr>
<th>Risk of Relapse</th>
<th>Adjusted OR, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mania</td>
<td></td>
</tr>
<tr>
<td>Depressed</td>
<td></td>
</tr>
<tr>
<td>Euthymic</td>
<td></td>
</tr>
</tbody>
</table>

### Differential Diagnosis of Bipolar Depression

Depressed patients with 1-5 previous mood episodes were 40% more likely to respond to therapy than those with >10 episodes (OR=1.6, 95% CI: 1.02-2.40).
Jerry

**Patient Background**

- 21-year-old waiter at local restaurant
  - Relocated to your area 3 months ago
  - Moved in with girlfriend after dating for 2 months
- Makes an appointment with you—his new PCP—after 21-year-old waiter at local restaurant
  - Treated with venlafaxine ER 75 mg once daily
  - Stopped taking his medication after 2 months
  - Symptoms resolved and he felt "like a new man"

MDD, major depressive disorder; PCP, primary care provider.

**Jerry

Initial Workup**

- Physical exam
  - Height, 5' 9"
  - Weight, 198 lb
  - Gained 5 lb last month
  - BMI, 29.2 kg/m²
  - Central adiposity
  - BP, 142/94 mm Hg
- Reports having 3-4 alcoholic drinks/day
  - Denies smoking or the use of any illicit drugs

Which factors in Jerry’s presentation suggest that his depressive symptoms are a result of bipolar disorder?

BMI, body mass index; BP, blood pressure; MI, myocardial infarction; T2DM, type 2 diabetes mellitus.

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**Bipolar Spectrum Disorders**

**Prevalence in the National Comorbidity Survey Replication**

<table>
<thead>
<tr>
<th>Disorder</th>
<th>12-Month Prevalence</th>
<th>Lifetime Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD with mania</td>
<td>0.30%</td>
<td>0.70%</td>
</tr>
<tr>
<td>MDD with hypomania</td>
<td>0.80%</td>
<td>1.60%</td>
</tr>
<tr>
<td>MDD with subthreshold symptoms</td>
<td>2.20%</td>
<td>6.70%</td>
</tr>
<tr>
<td>MDD only</td>
<td>5.40%</td>
<td>10.20%</td>
</tr>
</tbody>
</table>

**Progression to Bipolar Disorder**

From MDD

- 0.3% of patients converted to bipolar disorder during follow-up
- 0.5% of patients converted to bipolar disorder during follow-up
- 0.7% of patients converted to bipolar disorder during follow-up
- 0.9% of patients converted to bipolar disorder during follow-up
- 1.0% of patients converted to bipolar disorder during follow-up

19.6% of patients converted to bipolar disorder during follow-up

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**"Probabilistic" Approach to a Differential Diagnosis**

<table>
<thead>
<tr>
<th>Bipolar Depression (more likely with 9 or 21 present)</th>
<th>Unipolar Depression (more likely with 14 present)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia, more daytime sleeping</td>
<td>Initial insomnia or reduced sleep</td>
</tr>
<tr>
<td>Hyperphagia, increased body weight</td>
<td>Appetite or weight loss</td>
</tr>
<tr>
<td>Psychotic features during depression, pathologic guilt</td>
<td>Somatic complaints</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Normal or increased activity levels</td>
</tr>
<tr>
<td>Atypical symptoms (eg, labile personality)</td>
<td></td>
</tr>
<tr>
<td>Mood lability or manic symptoms</td>
<td></td>
</tr>
<tr>
<td>First depression &gt;25 years of age</td>
<td>First depression &gt;25 years of age</td>
</tr>
<tr>
<td>6 or more prior major depressive episodes</td>
<td>Long current episode (&gt;6 months)</td>
</tr>
<tr>
<td>Bipolar disorder in family history</td>
<td>No bipolar disorder in family history</td>
</tr>
</tbody>
</table>

Other factors that can help identify bipolar depression include:

- Sudden onset of symptoms
- Impulsivity
- Poor response of depressive symptoms to antidepressants

Identifying Bipolar Depression Screening and Diagnostic Considerations

- Assess duration, severity, and functional effects of mood symptoms
- Evaluate all patients with major depression for manic, hypomanic, and subthreshold symptoms
  - Ask about mood changes immediately before or after prior depressive episodes
  - Ask about prior periods of enhanced function
  - Ask about temporal relationship with antidepressant use
  - Specifically probe for suicidal ideation
- Consider screening tools
  - Mood Disorder Questionnaire
  - Bipolar Depression Rating Scale
- Obtain collateral history from a significant other
  - Relationship challenges between patient and significant others can complicate obtaining collateral information

Other references:

Assessing Patients With Suspected Bipolar Depression

**Type of Evaluation**

<table>
<thead>
<tr>
<th>Tests</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medical Tests</td>
<td>• Rule out or identify systemic illnesses, T2DM, hyperlipidemia</td>
</tr>
<tr>
<td></td>
<td>• Establish baseline for treatment with antipsychotics, lithium, anticonvulsants</td>
</tr>
<tr>
<td>Sleep Assessment</td>
<td>• Sleep disturbances may contribute to mood switching or relapse</td>
</tr>
<tr>
<td></td>
<td>• Standardizing sleep/wake schedules can improve outcomes</td>
</tr>
<tr>
<td>Suicide Risk Assessment</td>
<td>• Bipolar disorder associated with high suicide rates</td>
</tr>
<tr>
<td></td>
<td>• Evaluating and addressing suicidal ideation can be preventative</td>
</tr>
</tbody>
</table>

**Symptoms**

- *Hypomanic Episode (Bipolar II Disorder)*
  - Abnormally and persistently elevated mood, activity, and energy for 4 days
  - Clear change in functioning from usual nondepressed mood
  - Changes must be observable by others without marked impairment in social or occupational functioning
- *Manic Episode (Bipolar I Disorder)*
  - Abnormally and persistently elevated mood, activity, and energy for 1 week (less if there is hospitalization)
  - Must cause marked impairment in social or occupational functioning, require hospitalization, or include psychotic features

**Diagnosis of Bipolar Disorder**

**Changes in DSM-5**

<table>
<thead>
<tr>
<th>Core Symptoms</th>
<th>Elevated Mood</th>
<th>Elevated Mood + Depressed Mood or Loss of Interest</th>
<th>Depressed Mood or Loss of Interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>DSM-IV-TR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Manic</td>
<td>Mixed</td>
<td>Depressive with mixed features</td>
</tr>
<tr>
<td>DSM-5</td>
<td>Manic</td>
<td>Manic with mixed features</td>
<td>Depressive</td>
</tr>
</tbody>
</table>

In DSM-5, full manic or hypomanic episode may be identified when symptoms emerge during antidepressant treatment. Symptoms must persist beyond the physiologic effects of antidepressant drug.

**Diagnostic Differences Between Bipolar I and Bipolar II**

- Hypomanic Episode (Bipolar II Disorder)
  - Abnormally and persistently elevated mood, activity, and energy for 4 days
  - Clear change in functioning from usual nondepressed mood
  - Changes must be observable by others without marked impairment in social or occupational functioning
- Manic Episode (Bipolar I Disorder)
  - Abnormally and persistently elevated mood, activity, and energy for 1 week (less if there is hospitalization)
  - Must cause marked impairment in social or occupational functioning, require hospitalization, or include psychotic features

**Time to Switch in Trials of Antidepressants With Mood Stabilizers**

![Graph showing time to switch](image)

**Should Jerry return to his antidepressant therapy?**

Jerry is given a diagnosis of Bipolar I Disorder.

Jerry is a patient assessment and diagnosis.

- Lab results
  - A1C, 6.4%
  - TC, 207 mg/dL
  - LDL-C, 133 mg/dL
  - HDL-C, 44 mg/dL
  - TG, 160 mg/dL
  - Other lab results within normal range
  - MDQ, 9
  - PHQ-9, 18

- Phone interview with girlfriend confirms self-reported symptoms
  - Girlfriend recalls 2 “high-energy” periods for Jerry
  - Each lasting a week or more
  - Spent money impulsively
  - Sleeping habits irregular (eg, inconsistent bedtimes and days without sleep)
  - Currently sleeping through many weekend days

Jerry is given a diagnosis of Bipolar I Disorder.

Should Jerry return to his antidepressant therapy?
Other Risk Factors for Treatment-Emergent Affective Switching

- History of mania induced by an antidepressant
- Mixed depression
- Low TSH with TCA use
- Hyperthymic temperament
- TCA or SNRI use
  - NE active > 5-HT or DA
- Absence of antimanic mood stabilizer
- Genetic factors
- Substance abuse history
- Female gender + comorbid anxiety disorder

Antidepressants for Bipolar Depression

Combination Therapy With Mood Stabilizers

<table>
<thead>
<tr>
<th>Treatment-Emergent Affective Switch</th>
<th>Discontinuation of Study Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mood Stabilizer Plus Placebo</td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizer Plus Placebo</td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis of >3,000 patients showed no significant effects for antidepressant treatment on clinical response or remission.

Antidepressant Use in Bipolar Disorder

ISBD Task Force Recommendations

1. Adjunctive antidepressants for acute bipolar depression
   a. Permissible with history of positive antidepressant response
   b. Avoid in the presence of ≥2 core manic symptoms, psychomotor agitation, or rapid cycling

2. Antidepressant monotherapy for acute bipolar depression
   a. Avoid in bipolar I disorder
   b. Avoid in bipolar II disorder with ≥2 core manic symptoms

3. Adjunctive antidepressants for bipolar maintenance
   a. Permissible if patient relapses into depressive episode after stopping antidepressant therapy

Antidepressant Use in Bipolar Disorder (cont’d)

ISBD Task Force Recommendations

4. Antidepressant-induced switching and rapid cycling
   a. Discontinue antidepressants in response to switching or psychomotor agitation
   b. Discourage use with history of antidepressant-emergent mania/hypomania or mixed episodes
   c. Avoid if there is high mood instability or history of rapid cycling

5. Antidepressant use in mixed states
   a. Avoid during mood episodes with mixed features and in patients with predominately mixed states
   b. Discontinue if mixed state emerges

6. Antidepressant classes and increased risks of switching moods (SNRIs and TCAs)
   a. Permissible only after trials of other antidepressants
   b. Discourage use with history of antidepressant-emergent mania/hypomania or mixed episodes
   c. Avoid during mood episodes with mixed features and in patients with predominately mixed states
   d. Discontinue antidepressants in response to switching or mood destabilization required

Jerry

Clinical Overview

- Physical exam
  - Height, 5’9”
  - Weight, 196 lb
  - BMI, 29.2 kg/m² (overweight)
  - Significant central adiposity
  - BP, 142/94 mm Hg
  - Drinks 3-4 beers daily
  - Denies smoking and any illicit drug use
  - MDQ, 9
  - PHQ-9, 18
- Lab Results
  - A1c, 6.4%
  - TC, 207 mg/dL
  - LDL-C, 133 mg/dL
  - HDL-C, 44 mg/dL
  - TG, 160 mg/dL
  - Other lab results within normal range
- Family history
  - Father died of MI at 55 years
  - 56-year-old mother treated for T2DM and hypertension

How would you monitor Jerry’s cardiometabolic profile when managing his bipolar disorder?

Bipolar Disorder and Cardiovascular Risk

Risk Factors

- HDL-C, <40 mg/dL
- Triglycerides, >150 mg/dL
- FBG, >100 mg/dL
- BP, ≥140/90 mm Hg
- Waist circumference, ≥40 in Men, ≥35 in Women

How would you monitor Jerry’s cardiometabolic profile when managing his bipolar disorder?
Atypical Antipsychotics for Bipolar Depression
Evaluating the Evidence Base

<table>
<thead>
<tr>
<th>Drug</th>
<th>Recommended Daily Dose in Adults, mg/d</th>
<th>Notes on Therapeutic Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine</td>
<td>10–20</td>
<td></td>
</tr>
<tr>
<td>Olanzapine/fluoxetine combination</td>
<td>625–1250</td>
<td>Monitor metabolic profile (weight/BMI, lipids, glucose/A1c) and CBC.</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>20–120</td>
<td>Monitor metabolic profile, prolactin levels, and CBC.</td>
</tr>
</tbody>
</table>

- FDA approved for maintenance treatment
- FDA approved for bipolar depression

Jerry
Clinical Overview

- Physical exam
  - Weight, 5’9’’
  - Weight, 198 lb
  - Gained 5 lb last month
  - BMI, 29.2 kg/m² (overweight)
  - Significant central adiposity
  - BP, 142/84 mm Hg
- Drinks 3–4 beers daily
- Denies smoking and any illicit drug use
- MDQ, 9
- PHQ-9, 18
- Lab Results
  - A1c, 6.4%
  - TC, 207 mg/dL
  - LDL-C, 133 mg/dL
  - HDL-C, 44 mg/dL
  - TG, 160 mg/dL
  - Other lab results within normal range
- Family history
  - Father died of MI at 55 years
  - 56-year-old mother treated for T2DM and hypertension

How would you begin treating Jerry?

Quetiapine for Bipolar Depression
Two 8-Week Studies

BOLDER I Study
1

BOLDER II Study
2

All patients had bipolar I or II disorder and were experiencing a major depressive episode.

Olanzapine/Fluoxetine for Bipolar Depression
8-Week Study

<table>
<thead>
<tr>
<th>Group</th>
<th>MADRS Baseline Mean</th>
<th>MADRS Week 8 Mean</th>
<th>MADRS Mean Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine/Fluoxetine</td>
<td>20.5</td>
<td>8.2</td>
<td>-12.3</td>
</tr>
<tr>
<td>Placebo</td>
<td>20.5</td>
<td>11.2</td>
<td>-9.3</td>
</tr>
</tbody>
</table>

*p < 0.001 compared with placebo; **p < 0.01 compared with olanzapine alone.

Long-term Treatment With Lurasidone
Open-label Extension Study in Bipolar I Depression

<table>
<thead>
<tr>
<th>Group</th>
<th>MADRS Baseline Mean</th>
<th>MADRS Week 8 Mean</th>
<th>MADRS Mean Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>20.5</td>
<td>12.8</td>
<td>-7.7</td>
</tr>
<tr>
<td>Placebo</td>
<td>20.5</td>
<td>18.2</td>
<td>-2.3</td>
</tr>
</tbody>
</table>

Lurasidone monotherapy achieved a 44% greater reduction in depressive symptoms at Week 6 versus placebo.

Treatment-Emergent Adverse Effects

<table>
<thead>
<tr>
<th>Medication</th>
<th>Frequency/Number</th>
<th>Frequency/Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine/Fluoxetine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NNT and NNH

NNT: number of patients that need to be treated for 1 to benefit compared with control subjects

NNH: number of patients that need to be exposed to a risk factor (eg, study drug) for 1 patient to experience an adverse outcome compared with control subjects
Mood Stabilizers for Bipolar Depression

**Evaluating the Evidence Base**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily Dose Range, mg/d</th>
<th>Notes on Therapeutic Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>0.5-1.0 mEq/L</td>
<td>Serum levels should be monitored 12 h after a dose.</td>
</tr>
<tr>
<td>Valproate (divalproex sodium)</td>
<td>1000-2000 mg/d 50-120 µg/mL</td>
<td>Serum concentrations are best obtained at trough, ie, 12 h after last dose.</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>200 mg over 6 weeks</td>
<td>Watch for serious rash (prevalence 1-3 per 3000) and benign rash (~10% of patients).</td>
</tr>
</tbody>
</table>

*FDA approved for maintenance treatment

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Valproate for Acute Bipolar Depression

**Lithium for Acute Bipolar Depression**

Although lithium is not effective as monotherapy for acute bipolar depression, it is underutilized for bipolar disorder in US. Superior to valproate in the prevention of relapse. Antisuicidal effects at therapeutic levels. Increases neural survival factors (eg, BDNF) relative to apoptotic factors.

**MADRS Response Rates Across 6 Lamotrigine Multicenter Acute Bipolar Depression Studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Response Rates (%)</th>
<th>P Value (vs. Placebo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al 1999</td>
<td>Bipolar I (n=195)</td>
<td>54</td>
<td>29</td>
</tr>
<tr>
<td>SCA20910</td>
<td>Bipolar I and II</td>
<td>50</td>
<td>40</td>
</tr>
<tr>
<td>SCA40910</td>
<td>Bipolar I</td>
<td>46</td>
<td>39</td>
</tr>
<tr>
<td>SCA30924</td>
<td>Bipolar I</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td>SCA100223</td>
<td>Bipolar II</td>
<td>54</td>
<td>46</td>
</tr>
</tbody>
</table>

*Response defined as improvement over baseline in MADRS total score. Pooled relative risk of response 1.32 (1.06-1.64).

**Notes on Therapeutic Monitoring**

> Serum levels should be monitored 12 h after a dose.

**Mood Stabilizers for Bipolar Depression**

**Evaluating the Evidence Base**

**Recommendations for Pharmacotherapy of Acute Bipolar Depression**

<table>
<thead>
<tr>
<th>Depression Type</th>
<th>Monotherapy</th>
<th>Combination Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>De novo depression</td>
<td>Quetiapine, olanzapine, lurasidone, lamotrigine</td>
<td>Lithium + lamotrigine + olanzapine, lurasidone or valproate</td>
</tr>
<tr>
<td>Breakthrough depression</td>
<td>N/A</td>
<td></td>
</tr>
</tbody>
</table>

**TREATMENT GOALS**

Achieve complete remission, including full functional recovery and an absence of subsyndromal symptoms.

**Additional Challenges in Managing Bipolar Depression**

<table>
<thead>
<tr>
<th>Comorbid Anxiety Disorders</th>
<th>Cardiometabolic Issues</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substance Abuse</td>
<td>Poor Treatment Adherence</td>
</tr>
</tbody>
</table>

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Addressing Challenges in Bipolar Depression Management

- Highest rates of comorbid alcohol and substance abuse among axis I disorders
  - Elevates risk of suicide and rapid mood swings
  - Screen for substance abuse irrespective of other risk factors
  - Educate patients and family members
  - Consider preventive interventions and referrals for counseling
- Commonly comorbid with anxiety disorders
  - Elevates risk of suicide and mixed mood states
  - Anxiety symptoms may resolve with bipolar treatment
  - Among mood stabilizers, valproate has specific anxiolytic mechanism of action—GABA receptor stimulation
  - Recent data showed that lamotrigine significantly improved anxiety in patients with bipolar I disorder

When to Modify Therapy

- Switch therapy if patient is having intolerable side effects, such as excessive weight gain, akathisia, sedation and somnolence, or gastrointestinal issues
  - eg, consider switching if patient shows 25% increase in body weight, or development or worsening of T2DM or dyslipidemia
- Switch or augmentation therapy if the patient has entered a manic, hypomanic, or mixed manic state
- Modify therapy if serum levels are not in the desired therapeutic range
  - Lithium serum trough concentration, 0.8-1.2 mEq/L
  - Valproate serum trough concentration, 50-125 μg/mL
- eg, consider switching if patient shows ≥5% increase in body weight, akathisia, sedation and somnolence, or gastrointestinal issues

Evidence-Based Adjunctive Treatment in Bipolar Disorder

<table>
<thead>
<tr>
<th>Evidence-Based Therapy Interventions*</th>
<th>Corresponding Common Sense Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cognitive Behavioral Therapy</td>
<td>Help patients understand that cognitive distortions have a biological component</td>
</tr>
<tr>
<td>Interpersonal and Social Rhythm Therapy</td>
<td>Structure activities of daily living</td>
</tr>
<tr>
<td>Family-Focused Therapy</td>
<td>Help the family learn about the symptoms and genetics of the illness</td>
</tr>
<tr>
<td>Group Psychoeducation</td>
<td>Early recognition subsyndromal symptoms as predictors of relapse</td>
</tr>
</tbody>
</table>


Metabolic Risk of Select Agents for Bipolar Depression

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight</th>
<th>Dyslipidemia</th>
<th>Blood Pressure</th>
<th>Glucose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood Stabilizers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Valproate</td>
<td>↑</td>
<td>Inconsistent findings</td>
<td>↔</td>
<td>↓ (due to hypokalemia)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

Managing Bipolar Disorder in Primary Care

- Prepare your practice
  - Train staff
  - Build systems for appropriate follow-up
- Establish referral and other support networks
- Refer patients at risk for harming self or others to mental health services or emergency care
- Coordinate collaborative care with psychiatrists and other mental health care providers
- Provide patient and family members with local and national support networks
  - Depression and Bipolar Support Alliance
  - Work with patients to improve their adaptive, problem-solving, self-management, and self-monitoring skills

*Not approved by the US Food and Drug Administration as monotherapy for bipolar depression.


Screen for substance abuse irrespective of other risk factors


If a medication is discontinued, taper over at least 2 to 4 weeks to decrease the risks of a mood episode or suicide


Reasons for Nonadherence

- Dental of Illness
- Side Effects
- Failure to Recover from Illness
- Sense of Lack of Control Over Life
- Lapsed Prescription
- Cost of Medication
- Mixed Copays


Glucose

Hyperinsulinemia (due to increased appetite, increased glucose absorption, decreased insulin sensitivity, or increased insulin resistance, or increased insulin secretion, or decreased insulin clearance)
### Bipolar Depression

**Concluding Comments**

- **Assess all patients with depression for manic, hypomanic, and subthreshold symptoms**
  - Ask about mood changes immediately before or after prior depressive episodes
  - Ask about prior periods of enhanced function
  - Ask about temporal relationship with antidepressant use
  - Obtain collateral history from a significant other or family member
- **Perform risk-benefit assessment of pharmacologic interventions**
  - Evaluate whether patient suffers from acute or chronic depression
  - Consider existing cardiometabolic risks
  - Choose evidence-based treatments
- **Monitor patients carefully**
  - Monitor medical comorbidities and chronic insidious side effects (e.g., gradual weight gain)