Session 2: A Focus on Bipolar Depression: Overcoming Diagnostic Barriers and Optimizing Long-term Patient Outcomes

Learning Objectives

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.

Faculty

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Faculty Financial Disclosure Statements

The presenting faculty reported the following:


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**Suggested Reading List**


SESSION 2
9:15 – 10:30am
A Focus on Bipolar Depression:
Overcoming Diagnostic Barriers and
Optimizing Long-Term Patient
Outcomes

SPEAKERS
Joseph Calabrese, MD
Roger McIntyre, MD, FRCPC

A FOCUS ON
BIPOLAR DEPRESSION
Overcoming Diagnostic Barriers and
Optimizing Long-Term Patient
Outcomes

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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

Presenter Disclosure Information
The following relationships exist related to this presentation:


Off-Label/Investigational Discussion
► In accordance with prmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

Medications Discussed in Program
• Medication classes
  – Tricyclic antidepressants
  – SNRIs
  – SSRIs
  – Atypical antipsychotics
• Specific medications
  – Venlafaxine
  – Bupropion
  – Sertraline
  – Olanzapine
  – Olanzapine/fluoxetine
  – Quetiapine
  – Lurasidone
  – Lithium
  – Valtoperine (divalproex sodium)
  – Lamotrigine
  – Carbamazepine
SCI\text{E}NCI\text{F}IC INSIGHTS INTO BIPOLAR DISORDER

Michael E. Thase, MD
Professor
Department of Psychiatry
Director, Mood and Anxiety Disorders
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Symptom Status in Bipolar Disorder

\begin{tabular}{|c|c|c|}
\hline
Symptom Status & Bipolar I Disorder & Bipolar II Disorder \\
\hline
Asymptomatic & 9\% & 1\% \\
Manic & 53\% & 48\% \\
Depressed & 2\% & 2\% \\
Cycling/Mixed & 32\% & 1\% \\
\hline
\end{tabular}

Bipolar patients with bipolar disorder followed for an average of 12.4 years and 96 patients with bipolar II disorder followed for an average of 13.4 years.

Burden of Bipolar Depression

Key Points

- Affective episodes cause neurotoxicity and neural degeneration in the brain\textsuperscript{1-3}
  - Decreased BDNF levels and increased oxidative stress
- High risk of suicide\textsuperscript{4-7}
  - Suicidal ideation and attempts predominantly linked to depressive phase
- More depressive episodes associated with\textsuperscript{4,5}
  - Increased 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

\begin{tabular}{|c|c|c|}
\hline
Risk of Relapse & Adjusted OR, 95% CI \\
\hline
1-5 Episodes & \\
6-10 Episodes & \\
\hline
Risk of Relapse to Depression & \\
1-5 Episodes & \\
6-10 Episodes & \\
\hline
\end{tabular}

Depressed patients with 1-5 previous mood episodes were 49\% more likely to respond to therapy than those with >10 episodes (OR=1.49; 95\% CI: 1.02-2.04).\textsuperscript{9}

Differential Diagnosis of BIPOLAR DEPRESSION

Scientific Insights Into Bipolar Disorder

Key Points

- Bipolar disorder linked to aberrant connections and activity in limbic and cortical regions that process emotion\textsuperscript{1,2}
  - Disrupted emotional homeostasis and increased risks of extreme mood states
- Patients show altered signaling in circuits mediated by monoamines, glutamate, and GABA\textsuperscript{3}
  - Changes associated with impulsivity, psychosis, dysregulation, suicidality, and depression, among other clinical symptoms
- Clinical profiles of medications determined by affinities for and effects on various receptor subtypes\textsuperscript{4,5}
  - 5-HT1A agonism and 5-HT2A and dopaminergic antagonism tied 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

BDNF, brain-derived neurotrophic factor; FAST, Functioning Assessment Short Test.

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
  - girlfriend demanded that he seek help
- Frequently “too tired” and “unmotivated” to get up for work
- Repeatedly tardy and reprimanded for insubordination at work
- Sometimes sleeps all day on days off
- Current symptoms came on quickly after Jerry stayed up for multiple nights to work and paint new apartment
- MDD diagnosed 2 years ago from previous PCP
  - 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.

**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?

BML, 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>

N=9,282 adults assessed in a national household survey of the US population conducted between February 2001 and April 2003.

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**Progression to Bipolar Disorder From MDD**

- No bipolar disorder in family history
- Bipolar disorder in family history
- First depression <25 years of age
- First depression >25 years of age
- 5 prior major depressive episodes
- Long current episode (>6 months)
- Mood lability or manic symptoms
- Mood lability or manic symptoms (more likely with MDD with hypomania)
- Mood lability or manic symptoms (more likely with MDD with mania)
- Hyperphagia, increased body weight
- Psychotic features during depression, pathologic guilt
- Somatic complaints
- Fatigue, lack of energy
- Impairment or disability
- Decreased or increased appetite
- Impaired concentration or memory
- Sudden onset of symptoms
- Impulsivity
- Poor response of depressive symptoms to antidepressants

Other factors that can help identify bipolar depression include

- History of excessive or impulsive behavior
- History of mood swings
- History of alcohol or drug abuse
- History of suicide attempts or ideation
- History of family members with bipolar disorder

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

Bipolar Disord. 2008;10(1 Pt 2):144-152; Fiedorowicz JG, et al.
Bipolar Disord. 2007;9(6):571-579; Culpepper L.
Mood Disorder Questionnaire

1. Has there ever been a period of time when you were not your usual self and... YES NO
   - you were so irritable that you shouted at people or started fights or arguments?
   - ...you were much more talkative or spoke much faster than usual?
   - ...you got much less sleep than usual and found you didn't really miss it?
   - ...you felt much more self-confident than usual?
   - ...thoughts raced through your head or you couldn't slow your mind down?
   - ...you were so easily distracted by things around you that you had trouble in concentrating or staying on task?
   - ...you were much more social or outgoing than usual, for example, you telephoned friends in the middle of the night?
   - ...you were much more active or did many more things than usual?
   - ...you had much more energy than usual?
   - ...you did things that were unusual for you or that other people might have thought were excessive, foolish, or risky?
   - ...you were so depressed that you didn't want to get out of bed, or you didn't care what happened to you?
   - ...you were much more tired than usual and found you needed even more sleep than before?
   - ...you were so much less interested in things that you didn't care about what happened to you or the people around you?

A positive screen includes a score ≥7 from the 13 items listed above, co-occurrence of at least 2 items during the same period, and moderate or serious consequences of symptoms.

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>Manic</td>
<td>Manic with mixed features</td>
<td>Depressive</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

Assessing Patients With Suspected Bipolar Depression

<table>
<thead>
<tr>
<th>Type of Evaluation</th>
<th>Tests</th>
<th>Rationale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medical Tests</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete physical exam, PPG, lipid profile, CBC, prolactin levels</td>
<td>• Rule out or identify systemic illnesses, T2DM, hypertension</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Establish baseline for treatment with antidepressants, lithium, anticonvulsants</td>
</tr>
<tr>
<td><strong>Sleep Assessment</strong></td>
<td>Sleep logs</td>
<td>• Sleep disturbances may contribute to mood switching or relapse</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Standardizing sleep/wake schedules can improve outcomes</td>
</tr>
<tr>
<td><strong>Suicide Risk Assessment</strong></td>
<td>Columbia Suicide Severity Rating Scale, Suicide Behaviors Questionnaire-Revised</td>
<td>• Bipolar disorder associated with high suicide rates</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Evaluating and addressing suicidal ideation can be preventative</td>
</tr>
</tbody>
</table>

Jerry 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**
  - Girlfriends confirm initial symptoms
  - Girlfriends recall 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>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discontinue antidepressants in response to switching or rapid cycling</td>
<td>20</td>
</tr>
<tr>
<td>Avoid during mood episodes with mixed features and in patients with predominantly mixed episodes</td>
<td>30</td>
</tr>
<tr>
<td>Discontinue antidepressants in response to switching or rapid cycling</td>
<td>40</td>
</tr>
<tr>
<td>Avoid in bipolar I disorder</td>
<td>50</td>
</tr>
<tr>
<td>Avoid in bipolar II disorder with ≥2 core manic symptoms</td>
<td>60</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)**

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 predominantly 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

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

**Jerry Clinical Overview**

- **Physical exam**
  - Height, 5’ 9”
  - Weight, 198 lb
  - Gained 5 lb last month
  - 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

**Bipolar Disorder and Cardiovascular Risk**

- **Risk Factors**
  - High TG
  - Low HDL-C
  - High Blood Pressure
  - High Fasting Glucose
  - ≥3 Risk Factors, Metabolic Syndrome

- **Pharmacologic Therapy**
  - Large Waist Circumference
  - High TG
  - Low HDL-C
  - High Blood Pressure
  - High Fasting Glucose
  - ≥3 Risk Factors, Metabolic Syndrome

- **Women (n=104)**
  - Men (n=67)
  - 30.0
  - 31.5
  - 29.0

See ISBD Task Force description at http://www.isbd.org/task-forces/past-task-forces.
Bipolar Disorder and Metabolic Syndrome
Potentially Shared Etiology

Common risk factors and mechanisms identified in mood disorders and metabolic syndrome

- Insufficient access to primary and preventative health care
- Iatrogenic factors
- Habitual inactivity
- Neuroinflammation (e.g., proinflammatory cytokines)
- Oxidative stress
- Environmental hazards (e.g., early childhood adversity)

Bipolar disorder
MDD

Obesity
Hypertension
Dyslipidemia
Hyperglycemia


Monitoring Metabolic Risk in Bipolar Disorder

- Insufficient access to primary and preventative health care
- Iatrogenic factors
- Habitual inactivity
- Neuroinflammation (e.g., proinflammatory cytokines)
- Oxidative stress
- Environmental hazards (e.g., early childhood adversity)

Bipolar disorder
MDD

Obesity
Hypertension
Dyslipidemia
Hyperglycemia

• Recommend appropriate lifestyle and behavioral strategies to patients who are obese or have other cardiometabolic risk factors
  - eg, exercise, dietary changes, sleep hygiene, smoking cessation
• Consider cardiometabolic risks and metabolic liability of medications when prescribing therapy for bipolar disorder

Baseline 4
Weeks
8
Weeks
12
Weeks
Quarterly
Annually

Personal/Family History
X
X
X
X
X
X
X
X
X

Weight (BMI)
X
X
X
X
X
X
X
X
X

Waist Circumference
X
X
X
X
X
X
X
X
X

Blood Pressure
X
X
X
X
X
X
X
X
X

FPG
X
X
X
X
X
X
X
X
X

Fasting Lipids
X
X
X
X
X
X
X
X
X


Baseline 4
Weeks
8
Weeks
12
Weeks
Quarterly
Annually

Personal/Family History
X
X
X
X
X
X
X
X
X

Weight (BMI)
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X
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Waist Circumference
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Blood Pressure
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FPG
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Fasting Lipids
X
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X
X


Current Therapies for BIPOLAR DEPRESSION

- Physical exam
  - Height, 5’ 9’’
  - Weight, 198 lb
  - Gained 5 lb last month
  - BMI, 29.2 kg/m² (overweight)
  - Significant central adiposity
  - BP, 142/94 mm Hg
  - Drinks 3-4 beers daily
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    - A1c, 6.4%
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    - 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?
**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>Monitor metabolic profile (weight/BMI, lipids, glucose/A1c) and CBC.</td>
</tr>
<tr>
<td>Olanzapine/fluoxetine combination</td>
<td>6/25-12/50</td>
<td></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>

**Notes**
- "FDA approved for bipolar depression" and "FDA approved for maintenance treatment".
- Monitor CBC in patients with pre-existing low white blood cell count or history of leukopenia or neutropenia.

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**Olanzapine/Fluoxetine for Bipolar Depression**

**8-Week Study**

- Olanzapine Group (n=331)
- Olanzapine/Fluoxetine Group (n=82)

**Lurasidone for Bipolar Depression**

**8-Week Study**

- Monotherapy
- Adjunctive Therapy

**Long-term Treatment With Lurasidone**

**Open-label Extension Study in Bipolar I Depression**

**Treatment-Emergent Adverse Effects**

<table>
<thead>
<tr>
<th>Olanzapine/Fluoxetine Combination</th>
<th>Quetiapine</th>
<th>Lurasidone</th>
</tr>
</thead>
<tbody>
<tr>
<td>(20-50 mg, 50-100 mg or 120 mg)</td>
<td>(300 mg/600 mg)</td>
<td>(60 mg/120 mg)</td>
</tr>
</tbody>
</table>

- Somnolence (20.9%)<br>Sedation (42.7%/47.4%)<br>Headache (14.9%)<br>Weight gain (7.1%/19.5%)<br>Somatomania (17.2%/17.4%)<br>Diarrhoea (18.6%)<br>Somnolence (29.9%/19.3%)<br>Asaklole (7.9%/10.8%)<br>Dry mouth (18.3%)<br>EPS (13.2%/10.1%)<br>Dry mouth (6.1%/3.6%)<br>Headache (14.2%)<br>Fatigue (9.4%/11.3%)<br>EPS (4.9%/9.4%)<br>Increased appetite (12.8%)<br>Headache (8.8%/6.3%)<br>Somatomania (4.3%/6.8%)<br>Nausea (11.6%)<br>Constipation (2.6%/10.1%)<br>Somatomania (3.0%/2.7%)<br>Nervousness (9.3%)<br>Nausea (7.8%/7.0%)<br>Vomiting (2.4%/0.6%)<br>Insomnia (0.3%)<br>Weight gain (7.3%/3.9%/6.8%)

---

**Quetiapine for Bipolar Depression**

**Two 8-Week Studies**

- BOLDER I Study
- BOLDER II Study

**Notes on Treatment-Emergent Adverse Effects**
- Site effects are listed based on decreasing incidence with lower dose.
- EPS: extrapyramidal symptoms.
- All patients had bipolar I disorder and were experiencing a major depressive episode.
- {0.05} compared with placebo; {<0.01} compared with placebo; {<0.001} compared with placebo.

---

Divalproex sodium carries boxed warnings for hepatotoxicity and fetal risk (neural tube defects); the most common side effects were nausea, increased appetite, diarrhea, dry mouth, and cramps.


Although lithium is not effective as monotherapy for acute bipolar depression,1 it is underutilized for bipolar disorder in US. Superior to valproate in the prevention of relapse.2 Increases neural survival factors (eg, BDNF) relative to apoptotic factors.3

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>Titrate to lithium levels of 0.5-1.2 mg/d</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Serum levels should be monitored 12 h after a dose</td>
<td></td>
</tr>
<tr>
<td>Vaprapox</td>
<td>1000-2000 mg/d 50-120 µg/L</td>
<td>Serum concentrations are best obtained at trough 12 h after last dose</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Titrate to 200 mg over 6 weeks</td>
<td>Watch for serious rash (prevalence 1.3-3 per 1000) and benign rash (~10% of patients)</td>
</tr>
</tbody>
</table>

*FDA approved for maintenance treatment

**Lithium for Acute Bipolar Depression**

Mood stabilizers are effective in the acute treatment of bipolar depression and in the prevention of relapse.4

**Valproate for Acute Bipolar Depression**

- Placebo, n=28
- Divalproex ER, n=26

Week 0 Week 1 Week 2 Week 3 Week 4 Week 5 Week 6

MADRS, Least-Squares Mean Change From Baseline

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

<table>
<thead>
<tr>
<th>Study</th>
<th>Patient Population</th>
<th>Study</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></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SCAA2015</td>
<td>Bipolar I and II</td>
<td>54</td>
<td>29</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>SCA60910</td>
<td>Bipolar I</td>
<td>46</td>
<td>39</td>
<td>0.89</td>
</tr>
<tr>
<td>SCA39034</td>
<td>Bipolar I</td>
<td>46</td>
<td>40</td>
<td>0.42</td>
</tr>
<tr>
<td>SCA100223</td>
<td>Bipolar II</td>
<td>54</td>
<td>26</td>
<td>0.21</td>
</tr>
<tr>
<td>LamLit Study 2009**</td>
<td>Bipolar I (n=64) and II (n=48)</td>
<td>52</td>
<td>22</td>
<td>0.03</td>
</tr>
</tbody>
</table>

*Response rates in parenthesis are for Lamotrigine-treated patients.

**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><strong>De novo depression</strong>&lt;sup&gt;†&lt;/sup&gt;</td>
<td>• Quetiapine, olanzapine&lt;sup&gt;a&lt;/sup&gt;, lithium&lt;sup&gt;1&lt;/sup&gt;, lamotrigine&lt;sup&gt;1&lt;/sup&gt;, divalproex sodium&lt;sup&gt;1&lt;/sup&gt;</td>
<td>• Lithium + lamotrigine&lt;sup&gt;1&lt;/sup&gt; + Olanzapine + fluoxetine + lamotrigine + lithium or valproate</td>
</tr>
<tr>
<td><strong>Breakthrough depression</strong>&lt;sup&gt;‡&lt;/sup&gt;</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

<sup>1</sup> Depression episode occurs in the context of maintenance mood stabilizer treatment with a second medication

<sup>2</sup> Depression episode occurs in the context of ongoing mood stabilizing maintenance treatment

Not approved by the US Food and Drug Administration for acute episodes of bipolar depression

N=9,282 NCS-R respondents; comorbidities ordered by prevalence in bipolar I (impulse control disorders and phobias not shown).

### National Comorbidity Survey–Replication

<table>
<thead>
<tr>
<th>Axis I Comorbidity</th>
<th>Bipolar I Prevalence &amp; Risk (OR)</th>
<th>Bipolar II Prevalence &amp; Risk (OR)</th>
<th>Subthreshold Bipolar Prevalence &amp; Risk (OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any comorbidity</td>
<td>97.7% (47.7)</td>
<td>95.6% (24.5)</td>
<td>88.4% (8.5)</td>
</tr>
<tr>
<td>23 comorbidities</td>
<td>86.2% (112.3)</td>
<td>85.8% (38.3)</td>
<td>56.7% (14.3)</td>
</tr>
<tr>
<td>Any abuse/dependence</td>
<td>69.3% (8.8)</td>
<td>68.4% (21.5)</td>
<td>35.5% (3.3)</td>
</tr>
<tr>
<td>Alcohol abuse</td>
<td>56.2% (6.6)</td>
<td>36.0% (7.5)</td>
<td>33.2% (3.3)</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>48.3% (10.1)</td>
<td>27.3% (3.5)</td>
<td>22.9% (3.2)</td>
</tr>
<tr>
<td>Generalized anxiety</td>
<td>38.7% (8.9)</td>
<td>37.8% (7.7)</td>
<td>22.6% (4.3)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>38.9% (11.8)</td>
<td>19.9% (4.4)</td>
<td>18.9% (4.5)</td>
</tr>
<tr>
<td>PTSD</td>
<td>30.9% (6.6)</td>
<td>34.3% (7.3)</td>
<td>16.5% (3.6)</td>
</tr>
<tr>
<td>Drug dependence</td>
<td>30.4% (12.2)</td>
<td>8.7% (5.1)</td>
<td>8.9% (3.4)</td>
</tr>
<tr>
<td>Panic disorder</td>
<td>29.1% (9.4)</td>
<td>27.2% (8.1)</td>
<td>13.1% (3.3)</td>
</tr>
<tr>
<td>OCD</td>
<td>25.2% (21.4)</td>
<td>20.3% (16.7)</td>
<td>4.3% (3.9)</td>
</tr>
</tbody>
</table>

### Probability of First Suicide Attempt

Relationship With Number of Comorbid Mental/Substance Use Disorders

- **Any 1 Mental Illness**: 3.7
- **2 Comorbid Mental Illnesses**: 6.8
- **3 Comorbid Mental Illnesses**: 12.1
- **4 Comorbid Mental Illnesses**: 29.0

Among 16 DSM mental disorders, the risk of a suicide attempt was lowest in agoraphobia (OR=2.7) and highest in bipolar disorder (OR=6.7)

### Addressing Challenges in Bipolar Depression Management

- Highest rates of comorbid alcohol and substance abuse among axis I disorders<sup>1</sup>
  - 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<sup>2,4</sup>
  - 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 lurasidone significantly improved anxiety in patients with bipolar I disorder

### 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>

### 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>Lithium&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑</td>
<td>✫</td>
<td>✫</td>
<td>✫</td>
</tr>
<tr>
<td>Valproate&lt;sup&gt;†&lt;/sup&gt;</td>
<td>↑</td>
<td>✫</td>
<td>✫</td>
<td>✫ (due to hyperinsulinemia)</td>
</tr>
<tr>
<td>Lamotrigine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>✫</td>
<td>✫</td>
<td>✫</td>
<td>✫</td>
</tr>
<tr>
<td>Carbamazepine&lt;sup&gt;1&lt;/sup&gt;</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>Quetiapine&lt;sup&gt;1&lt;/sup&gt;</td>
<td>✫</td>
<td>✫</td>
<td>✫</td>
<td>✫</td>
</tr>
</tbody>
</table>

<sup>1</sup> Not approved by the US Food and Drug Administration for maintenance therapy in bipolar depression

<sup>†</sup> Consider preventive interventions and referrals for counseling

<sup>a</sup> Depression episode occurs in the context of ongoing mood stabilizing maintenance treatment

<sup>‡</sup> Depression episode occurs in the context of maintenance mood stabilizer treatment with a second medication

<sup>1</sup> Depression episode occurs in the context of maintenance mood stabilizer treatment with a second medication

<sup>2</sup> Recent data showed that lurasidone significantly improved anxiety in patients with bipolar I disorder

<sup>4</sup> Depression episode occurs in the context of ongoing mood stabilizing maintenance treatment
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
  - e.g., consider switching if patient shows ≥5% 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

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


Evidence-Based Adjunctive Treatment in Bipolar Disorder

- Cognitive Behavioral Therapy
- Interpersonal and Social Rhythm Therapy
- Family-Focused Therapy
- Group Psychoeducation

<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 subprodromal symptoms as predictors of relapse</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


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)