Improving the Recognition and Treatment of Bipolar Depression
Learning Objectives

• Apply evidence-based tools that aid in differentiating patients with bipolar depression from those with unipolar depression

• Interpret efficacy and safety data for current and emerging therapies for bipolar depression

• Implement treatment strategies to enhance adherence and improve patient functioning during the long-term maintenance stage
Pre-Poll Question

I feel competent managing patients with bipolar depression.

1. Strongly Disagree
2.
3.
4.
5. Strongly Agree
A 28-year-old woman presents with a depressive episode. She has previously been hospitalized and treated for a manic episode but is not currently taking any medication. The agents with the strongest evidence of efficacy in bipolar depression are:

1. Lamotrigine, lithium, quetiapine
2. Quetiapine, olanzapine-fluoxetine, lurasidone
3. Olanzapine-fluoxetine, lurasidone, lamotrigine
4. Lurasidone, lamotrigine, lithium
DIFFERENTIAL DIAGNOSIS
Diagnostic Conversion From MDD to BD

- Non-Converters: 67.2%
- Converters: 32.8%

Characteristics of Patients With Diagnostic Conversion From MDD to BD

***p<0.0005
Characteristics of Patients With Diagnostic Conversion From MDD to BD

***p<0.0005

Subthreshold Hypomania in MDD

• Up to 40% of patients diagnosed with unipolar depression have symptoms of hypomania
  – Most common symptoms
    • Irritability, mental overactivity, psychomotor agitation, talkativeness

• High impulsivity increases the rate of conversion to BPI or BPII

• BPII vs. MDD: distinct disorders or continuity on the mood spectrum?

## Bipolar II Disorder vs. Major Depressive Disorder

<table>
<thead>
<tr>
<th>Variables</th>
<th>BP-II (n=389)</th>
<th>MDD (n=261)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (years)</td>
<td>41.3 (12.9)</td>
<td>46.8 (14.8)</td>
<td>0.7 (0.6–0.8)*</td>
</tr>
<tr>
<td>Age at onset first MDE (years)</td>
<td>22.8 (10.6)</td>
<td>31.8 (13.8)</td>
<td>0.5 (0.4–0.6)*</td>
</tr>
<tr>
<td>Females (%)</td>
<td>67.0</td>
<td>61.6</td>
<td>1.2 (0.9–1.7)</td>
</tr>
<tr>
<td>≥5 MDEs (%)</td>
<td>78.9</td>
<td>58.2</td>
<td>2.6 (1.8–3.7)*</td>
</tr>
<tr>
<td>MDE symptoms &gt;2 years (%)</td>
<td>37.5</td>
<td>34.8</td>
<td>1.1 (0.8–1.5)</td>
</tr>
<tr>
<td>Axis I comorbidity (%)</td>
<td>54.2</td>
<td>47.5</td>
<td>1.3 (0.9–1.7)</td>
</tr>
<tr>
<td>Psychotic features (%)</td>
<td>7.7</td>
<td>8.4</td>
<td>0.9 (0.5–1.6)</td>
</tr>
<tr>
<td>Melancholic features (%)</td>
<td>12.0</td>
<td>13.0</td>
<td>0.9 (0.5–1.4)</td>
</tr>
<tr>
<td>Atypical depression (%)</td>
<td>52.6</td>
<td>28.7</td>
<td>2.7 (1.9–3.8)*</td>
</tr>
<tr>
<td>Mixed depression (%)</td>
<td>64.5</td>
<td>32.1</td>
<td>3.8 (2.7–5.3)*</td>
</tr>
<tr>
<td>GAF (range)</td>
<td>50.2 (9.2)</td>
<td>50.9 (9.6)</td>
<td>0.9 (0.8–1.0)</td>
</tr>
<tr>
<td>Bipolar I or II family history (%)</td>
<td>44.7</td>
<td>15.3</td>
<td>4.4 (2.8–7.0)*</td>
</tr>
</tbody>
</table>

*p<0.01

## Differential Symptom Profile for Unipolar vs. Bipolar Depression?

<table>
<thead>
<tr>
<th>Symptom</th>
<th>MDD (n=52): % with indicator</th>
<th>Bipolar (n=52): % with indicator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychomotor slowing</td>
<td>52</td>
<td>83</td>
</tr>
<tr>
<td>Self-blame, worthlessness</td>
<td>29</td>
<td>52</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>10</td>
<td>25</td>
</tr>
<tr>
<td>Increased weight</td>
<td>6</td>
<td>19</td>
</tr>
<tr>
<td>Leaden paralysis</td>
<td>69</td>
<td>87</td>
</tr>
<tr>
<td>Early morning insomnia</td>
<td>67</td>
<td>44</td>
</tr>
<tr>
<td>Hypersomnia</td>
<td>17</td>
<td>27</td>
</tr>
<tr>
<td>Interpersonal sensitivity</td>
<td>65</td>
<td>81</td>
</tr>
</tbody>
</table>

"Probabilistic" Approach to Differentiating Between Bipolar and Unipolar Depression

<table>
<thead>
<tr>
<th>Suspect bipolar depression if</th>
<th>Suspect unipolar depression if</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia and/or increased daytime napping</td>
<td>Initial insomnia/reduced sleep</td>
</tr>
<tr>
<td>Hyperphagia and/or increased weight</td>
<td>Appetite loss and/or weight loss</td>
</tr>
<tr>
<td>Other atypical depressive symptoms (e.g., leaden paralysis)</td>
<td></td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td>Normal or increased activity level</td>
</tr>
<tr>
<td>Psychotic features and/or pathological guilt</td>
<td>Somatic complaints</td>
</tr>
<tr>
<td>Mood lability</td>
<td></td>
</tr>
<tr>
<td>Early onset of first depression (&lt;25 years?)</td>
<td>Later onset of first depression (&gt;25 years?)</td>
</tr>
<tr>
<td>Multiple prior episodes (&gt;4?)</td>
<td>Long duration of current episode (&gt;6 months?)</td>
</tr>
<tr>
<td>Positive family history of bipolar disorder</td>
<td>Negative family history of bipolar disorder</td>
</tr>
</tbody>
</table>

Stahl SM. CNS Spectrums; in press.
TREATMENT OF BIPOLAR DEPRESSION: EFFICACY
Depression-Minded Treatments

- treat from below
- stabilize from below

HYPOMANIA

DYSRHYTHMIA

stabilize from below

treat from below
Bipolar Depression: What's Available

- lithium
- carbamazepine
- lamotrigine
- oxcarbazepine
- valproate
- aripiprazole
- asenapine
- iloperidone
- lurasidone
- olanzapine
- paliperidone
- quetiapine
- risperidone
- ziprasidone
- OFC
- bupropion
- fluoxetine
- paroxetine
- other ADs
Bipolar Depression: What's (Relatively) Well Studied

- lithium
- carbamazepine
- aripiprazole
- lamotrigine
- fluoxetine
- bupropion
- valproate
- paroxetine
- quetiapine
- olanzapine
- ziprasidone

Bipolar Depression: What Has Consistent Positive Evidence

- lurasidone
- quetiapine
- OFC

## Bipolar Depression: What's Recommended First-Line (Summary)

<table>
<thead>
<tr>
<th>WFSBP</th>
<th>BAP</th>
<th>ISBD</th>
<th>CANMAT</th>
<th>NICE</th>
</tr>
</thead>
<tbody>
<tr>
<td>lithium</td>
<td>lithium</td>
<td>lithium</td>
<td>lithium</td>
<td>lithium</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>lamotrigine (adj)</td>
</tr>
<tr>
<td>valproate</td>
<td>valproate</td>
<td></td>
<td>valproate (w Li+)</td>
<td></td>
</tr>
<tr>
<td>olanzapine</td>
<td></td>
<td></td>
<td>olanzapine (w SSRI)</td>
<td></td>
</tr>
<tr>
<td>quetiapine</td>
<td>quetiapine</td>
<td>quetiapine</td>
<td>quetiapine</td>
<td>quetiapine (adj)</td>
</tr>
<tr>
<td>OFC</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

ADs

SSRIs, BUP (adj)

SSRIs (adj)

Bipolar Depression: NEI Practice Guideline

- On VAL
  - Add/switch to Li, LAM, QUE, or LUR

- On Li
  - Add/switch to LAM, QUE, or LUR

- On atypical antipsychotic (QUE or LUR)
  - Add/switch to LAM
  - Add/switch to Li
  - Switch to OLZ + SSRI
  - Add Li or LAM
  - Add Li or LAM

- Not on medication
  - Add VAL
  - Add Li + VAL

Stahl SM. CNS Spectraums; in press.
Mood Stabilizers: Recommended Doses in Bipolar Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
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<tbody>
<tr>
<td>lamotrigine (mono)</td>
<td>100–200 mg</td>
</tr>
<tr>
<td>lithium</td>
<td>0.6–1.0 mEq/L</td>
</tr>
<tr>
<td>lurasidone</td>
<td>20–120 mg</td>
</tr>
<tr>
<td>olanzapine-fluoxetine</td>
<td>6–12/25–50 mg</td>
</tr>
<tr>
<td>quetiapine</td>
<td>300 mg</td>
</tr>
<tr>
<td>valproate</td>
<td>70–90 mg/L</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>aripiprazole</td>
<td>15–30 mg (maint)</td>
</tr>
<tr>
<td>asenapine</td>
<td>5–10 mg (maint)</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>4–15 mg/L (maint)</td>
</tr>
<tr>
<td>iloperidone</td>
<td>12–24 mg (maint)</td>
</tr>
<tr>
<td>oxcarbazepine</td>
<td>1200–2400 mg (mania)</td>
</tr>
<tr>
<td>paliperidone</td>
<td>6 mg (schiz)</td>
</tr>
<tr>
<td>risperidone</td>
<td>25–50 mg IM q2wks (maint)</td>
</tr>
<tr>
<td>ziprasidone</td>
<td>80–160 mg (maint)</td>
</tr>
</tbody>
</table>
What's the Role of Antidepressants? 
Recent Recommendations From ISBD

• When to avoid ADs
  – As adjunct for acute bipolar I or II depressive episode with ≥2 concomitant manic Sx, psychomotor agitation, or rapid cycling
  – As monotherapy in bipolar I disorder
  – As monotherapy in bipolar II depression with ≥2 concomitant manic Sx
  – During manic and depressive episodes with mixed features
  – In patients with predominantly mixed states

What's the Role of Antidepressants?  
Recent Recommendations From ISBD

- When to consider ADs
  - As adjunct for acute bipolar I or II depressive episode in patients with a history of good AD response
  - As maintenance (adjunct) for patients who relapse into a depressive episode after stopping an AD

Psychotherapy With Positive Evidence (Adjunct)

- Interpersonal and social rhythm therapy
  - Focuses on the social situations that may involve stressors/triggers
  - Promotes organized lifestyle, including ordered sleep schedule

- Psychoeducation
  - Regarding symptoms, disease course, treatment, coping methods
  - During euthymic stage
  - Helps with early episode detection and treatment adherence

Psychotherapy With Positive Evidence (Adjunct)

- Family therapy
  - Psychoeducation
  - Communication and problem solving skills

- Cognitive behavioral therapy
  - Modifies cognitive distortions

- Systematic care model
  - Use psychoeducation to promote active patient participation in treatment
  - Promote easy access to medical services

Most studies show positive results

Studies not specific to bipolar depression

Unclear which interventions may be preferable for which presentations of the disorder

– Stage, duration, comorbidities

Lolich M. Actas Esp Psiquiatr 2012;40(2):84-92;
Cautiously consider adding bupropion

Add modafinil, armodafinil, or pramipexole

Cautiously consider adding bupropion

Replace one or both agents with alternate first- or second-line agents

Consider ECT, third-line agents, and novel or experimental options

Stahl SM. CNS Spectrums; in press.
TREATMENT OF BIPOLAR DEPRESSION: SAFETY AND TOLERABILITY
<table>
<thead>
<tr>
<th></th>
<th>LMG</th>
<th>LI</th>
<th>LUR</th>
<th>OLZ</th>
<th>QUET</th>
<th>VAL</th>
<th>Other</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>rash</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>tremor, GI, acne, thyroid, renal</td>
</tr>
<tr>
<td></td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>0</td>
<td>tremor, GI</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>+</td>
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</tr>
</tbody>
</table>

Mood Stabilizers: Side Effects (cont.)

<table>
<thead>
<tr>
<th></th>
<th>Mood Stabilizers</th>
<th>Side Effects</th>
<th>Other</th>
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<tbody>
<tr>
<td>ARIP</td>
<td>+</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>ASEN</td>
<td>+</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>CBZ</td>
<td>0</td>
<td>+++</td>
<td>0</td>
</tr>
<tr>
<td>ILOP</td>
<td>0</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>OXC</td>
<td>0</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>PAL</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>RSP</td>
<td>++</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>ZIP</td>
<td>+</td>
<td>+</td>
<td>0</td>
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</tbody>
</table>

Metabolic Changes With Olanzapine and Quetiapine: Total Cholesterol (mg/dL)

Metabolic Changes With Olanzapine and Quetiapine: Glucose (mg/dL)

Metabolic Changes With Lurasidone

**Cholesterol**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change From Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=147)</td>
<td>197.4 mg/dL</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg (n=140)</td>
<td>196.0 mg/dL</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=144)</td>
<td>202.2 mg/dL</td>
</tr>
<tr>
<td>BL Mean</td>
<td>197.4 mg/dL</td>
</tr>
</tbody>
</table>

**Triglycerides**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change From Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=147)</td>
<td>125.2 mg/dL</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg (n=140)</td>
<td>132.4 mg/dL</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=144)</td>
<td>133.9 mg/dL</td>
</tr>
<tr>
<td>BL Mean</td>
<td>125.2 mg/dL</td>
</tr>
</tbody>
</table>

Safety Population

Metabolic Changes With Lurasidone

Safety Population

Median Change From Baseline (mg/dL)

Glucose

Placebo (n=148)
Lurasidone 20-60 mg (n=140)
Lurasidone 80-120 mg (n=143)

BL Mean
Safety Population
94.5 mg/dL
94.3 mg/dL
94.7 mg/dL

# Mood Stabilizers: Monitoring Guidelines

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline</th>
<th>Monthly</th>
<th>3 Months</th>
<th>6 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>D, C</td>
<td>C**</td>
<td>D***</td>
<td></td>
<td>D, C</td>
</tr>
<tr>
<td>Renal</td>
<td>L</td>
<td>C**</td>
<td>L</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>CBC</td>
<td>C</td>
<td>C**</td>
<td>D***</td>
<td></td>
<td>C, D</td>
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<tr>
<td>Menstrual change</td>
<td></td>
<td></td>
<td>D***</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium</td>
<td></td>
<td></td>
<td></td>
<td>L</td>
<td>L</td>
</tr>
<tr>
<td>Serum levels*</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight</td>
<td>D, A</td>
<td>A**</td>
<td>D***, A</td>
<td>L</td>
<td>L, D, A</td>
</tr>
<tr>
<td>BP</td>
<td>A</td>
<td></td>
<td></td>
<td>A***</td>
<td>A</td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>A</td>
<td></td>
<td></td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>A</td>
<td></td>
<td></td>
<td>A</td>
<td>A</td>
</tr>
</tbody>
</table>

L: lithium  
D: divalproex  
C: carbamazepine  
A: atypical antipsychotic  

*Stable patients  
**For first 3 months of treatment  
***For first year of treatment

BIPOLAR MAINTENANCE
Bipolar Maintenance: What’s Available

- lithium
- carbamazepine
- lamotrigine
- oxcarbazepine
- valproate
- aripiprazole
- asenapine
- iloperidone
- lurasidone
- olanzapine
- paliperidone
- quetiapine
- risperidone
- ziprasidone
- OFC
- psychotherapy
- psychoeducation
Bipolar Maintenance: What's (Relatively) Well Studied

- lithium
- carbamazepine
- lamotrigine
- valproate
- aripiprazole
- psychotherapy
- olanzapine
- quetiapine
- risperidone
- ziprasidone
- psychoeducation

Bipolar Maintenance: What Has Consistent Positive Evidence

- lithium
- lamotrigine
- valproate
- aripiprazole
- olanzapine
- quetiapine
- risperidone*
- psychotherapy
- psychoeducation

*Injectable

Bipolar Maintenance: What's Recommended

- Aripiprazole*
- Risperidone***
- Quetiapine
- Lithium*
- Lamotrigine**
- Valproate*
- Olanzapine*
- Ziprasidone

- Lithium
- Lamotrigine
- Valproate
- Aripiprazole*
- Olanzapine
- Quetiapine
- Risperidone***

*Predominantly mania
**Predominantly depression
***Injectable

## NEI Practice Guideline: Choice of Long-term Medications

Continue current medication if effective. Otherwise, consider (alphabetical order):

<table>
<thead>
<tr>
<th>Maintenance Medication to Prevent</th>
<th>Manic Relapse</th>
<th>Depressive Relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Lithium</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>✓</td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td>✓</td>
<td>✓✓✓</td>
</tr>
<tr>
<td>Valproate</td>
<td>✓</td>
<td>✓✓</td>
</tr>
</tbody>
</table>

Stahl SM. CNS Spectrums: in press.
NEI Practice Guideline: Residual Symptoms or Relapse

- If the burden of disease is mania
  - Consider combining predominantly anti-manic agents (e.g., lithium, valproate, antipsychotic)

- If the burden of disease is depression
  - Lamotrigine, quetiapine, or lurasidone
    - Lamotrigine may require combination with an anti-manic

- Consider clozapine in treatment-refractory patients

- Consider long-acting depot antipsychotics for frequently relapsing bipolar disorder

Stahl SM. CNS Spectrums; in press.
Reasons for Nonadherence

• Forgetting to take dose
• Side effects
• Insufficient illness knowledge
• Family/friends who advise against medication
• Access problems
• Alcohol and drug use

Sajatovic M. Compr Psychiatry 2011;52:280-7;
Interventions to Improve Adherence

• Most effective interventions only lead to small improvement in adherence or outcomes
  – More convenient care
  – Reminders
  – Self-monitoring
  – Reinforcement
  – Counseling
  – Family therapy
  – Psychological therapy
  – Crisis intervention
  – Telephone follow-up

Bipolar Maintenance: General Management

• Maintain medication
  – Educate on chronicity of disorder
  – Help establish routine for taking medication

• Maintain psychoeducation and psychotherapy
  – Include caregiver psychoeducation

• Monitor for and address adverse effects

• Encourage regular physical and social activity

• Encourage regular sleep pattern

• Address interepisode impairment
  – Neurocognitive, difficulty with sustained attention
  – Sleep disturbance

Bipolar Maintenance: General Management

• Train to monitor for prodromal symptoms
  – Change in motivated activity, sleep cycle, impulsivity, or interpersonal behavior
  – Change in affect (usually later in prodromal stage)
  – Usually consistent within individual

• Train to address prodromal symptoms
  – Small medication adjustment
  – Change in daily routine
  – Stress reduction
  – Increase in social interaction

Summary

- The evidence base for the treatment and maintenance of bipolar depression is relatively weak, and practice guidelines differ.

- The 3 agents with the most evidence of efficacy for bipolar depression are quetiapine, olanzapine-fluoxetine, and lurasidone.

- More agents have evidence of preventing manic and/or depressive relapse.

- Patient and family education are integral, particularly monitoring for and addressing prodromal symptoms.