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
Pretest Question

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

*\textit{p}<0.05

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?

Progression to Bipolar Disorder


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## 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>
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</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>41.3 (12.9)</td>
<td>46.8 (14.8)</td>
<td>0.7 (0.6–0.8)*</td>
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<tr>
<td>Age at onset first MDE</td>
<td>22.8 (10.6)</td>
<td>31.8 (13.8)</td>
<td>0.5 (0.4–0.6)*</td>
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<tr>
<td>Females</td>
<td>67.0</td>
<td>61.6</td>
<td>1.2 (0.9–1.7)</td>
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<tr>
<td>≥5 MDEs</td>
<td>78.9</td>
<td>58.2</td>
<td>2.6 (1.8–3.7)*</td>
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<tr>
<td>MDE symptoms &gt;2 years</td>
<td>37.5</td>
<td>34.8</td>
<td>1.1 (0.8–1.5)</td>
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<tr>
<td>Axis I comorbidity</td>
<td>54.2</td>
<td>47.5</td>
<td>1.3 (0.9–1.7)</td>
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<tr>
<td>Psychotic features</td>
<td>7.7</td>
<td>8.4</td>
<td>0.9 (0.5–1.6)</td>
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<tr>
<td>Melancholic features</td>
<td>12.0</td>
<td>13.0</td>
<td>0.9 (0.5–1.4)</td>
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<tr>
<td>Atypical depression</td>
<td>52.6</td>
<td>28.7</td>
<td>2.7 (1.9–3.8)*</td>
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<tr>
<td>Mixed depression</td>
<td>64.5</td>
<td>32.1</td>
<td>3.8 (2.7–5.3)*</td>
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<tr>
<td>GAF</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>
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</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>
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<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>
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<tr>
<td>Increased weight</td>
<td>6</td>
<td>19</td>
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<tr>
<td>Leaden paralysis</td>
<td>69</td>
<td>87</td>
</tr>
<tr>
<td>Early morning insomnia</td>
<td>67</td>
<td>44</td>
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<tr>
<td>Hypersomnia</td>
<td>17</td>
<td>27</td>
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<tr>
<td>Interpersonal sensitivity</td>
<td>65</td>
<td>81</td>
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</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>Normal or increased activity level</td>
</tr>
<tr>
<td>Psychomotor retardation</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

- HYPOMANIA
- DYSTHYMIA

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
- fluoxetine
- paroxetine
- other ADs

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Bipolar Depression: What's (Relatively) Well Studied

- lithium
- carbamazepine
- lamotrigine
- aripiprazole
- valproate
- lurasidone
- olanzapine
- quetiapine
- ziprasidone
- fluoxetine
- paroxetine
- OFC

Bipolar Depression: What Has Consistent Positive Evidence

Quetiapine in Bipolar Depression

Study
Calabrese et al. 2005
Thase et al. 2006
Young et al. 2010
McElroy et al. 2010

**Quetiapine 600 pooled**
Heterogeneity: $Q=3.64; p=0.303$
Overall: $Z=-7.71; p=0; n=1396$

Calabrese et al. 2005
-6.13 (-8.33; -3.93)
Thase et al. 2006
-5.01 (-6.95; -3.07)
Young et al. 2010
-3.55 (-5.55; -1.55)
McElroy et al. 2010
-3.59 (-6.1; -1.08)

**Suppes et al. 2010**

**Quetiapine 200 pooled**
Heterogeneity: $Q=4.19; p=0.381$
Overall: $Z=-9.37; p=0; n=1661$

-5.51 (-7.88; -3.14)

MADRS WMD (95% CI)

$-6.47 (-8.67; -4.27)$
$-4.07 (-6.03; -2.11)$
$-4.29 (-6.28; -2.3)$
$-3.71 (-6.22; -1.2)$
$-4.64 (-5.82; -3.46)$

Favors: QUET PBO


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OFC in Bipolar Depression

Data from two 8-week randomized clinical trials for bipolar depression. Primary measure was change in MADRS; OFC was significantly superior to both OLZ and PBO. OFC: n=86, mean daily dose 7.4 mg/39.3 mg. OLZ: n=370, mean daily dose 9.7 mg. PBO: n=377. Citrome L. Expert Opinion Pharmacother 2011;12(17):2751-8.
Lurasidone in Bipolar Depression: Monotherapy


Effect size (MMRM)
Lurasidone 20-60 mg: 0.51
Lurasidone 80-120 mg: 0.51

Placebo (n=162)
Baseline mean = 30.5

Lurasidone 20-60 mg (n=161)
Baseline mean = 30.3

Lurasidone 80-120 mg (n=162)
Baseline mean = 30.6

*p<0.05  **p<0.01  ***p<0.001
Lurasidone in Bipolar Depression: Adjunct

Change From Baseline in MADRS (MMRM)

Effect size: 0.34 (MMRM)

- Placebo + Li/VPA (N=161)
  - Baseline mean = 30.8

- Lurasidone + Li/VPA (N=179)
  - Baseline mean = 30.6

Mean daily dose of lurasidone: 66.3 mg (90% of participants received ≥60 mg)

*p<0.05  **p<0.01  ***p<0.001

### 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>
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<tbody>
<tr>
<td>lithium</td>
<td>lithium</td>
<td>lithium</td>
<td>lithium</td>
<td>lamotrigine (adj)</td>
</tr>
<tr>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>lamotrigine</td>
<td>valproate (w Li+)</td>
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<tr>
<td>valproate</td>
<td>valproate</td>
<td></td>
<td></td>
<td>olanzapine (w SSRI)</td>
</tr>
<tr>
<td>olanzapine</td>
<td>quetiapine</td>
<td>quetiapine</td>
<td>quetiapine</td>
<td>quetiapine (adj)</td>
</tr>
<tr>
<td>ADs</td>
<td></td>
<td></td>
<td></td>
<td>SSRIs, BUP (adj)</td>
</tr>
</tbody>
</table>

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

Not on medication
- Add VAL
- Add Li + VAL

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

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<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
### Meta-analysis: BP Remission With Antidepressant vs. Placebo

Studies were 16 weeks or less.


<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant, n/N</th>
<th>Placebo, n/N</th>
<th>Relative Risk (fixed), 95% CI</th>
<th>Weight, %</th>
<th>Relative Risk (fixed), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al(^4) (1989)</td>
<td>30/59</td>
<td>5/27</td>
<td>[2.75 (1.20–6.30)]</td>
<td>5.13</td>
<td></td>
</tr>
<tr>
<td>Shelton and Stahl(^4) (2004)</td>
<td>5/20</td>
<td>3/10</td>
<td>[0.83 (0.25–2.80)]</td>
<td>2.99</td>
<td></td>
</tr>
<tr>
<td>Tohen et al(^2) (2003)</td>
<td>46/82</td>
<td>137/351</td>
<td>[1.44 (1.14–1.81)]</td>
<td>38.77</td>
<td></td>
</tr>
<tr>
<td>Amsterdam et al(^4) (2005)</td>
<td>3/17</td>
<td>1/8</td>
<td>[1.41 (0.17–11.54)]</td>
<td>1.02</td>
<td></td>
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<tr>
<td>Sachs et al(^9) (2007)</td>
<td>58/163</td>
<td>71/169</td>
<td></td>
<td>52.09</td>
<td>[0.85 (0.65–1.11)]</td>
</tr>
</tbody>
</table>

Total (95% CI): 341 antidepressant, 565 placebo

Test for heterogeneity: \(\chi^2 = 12.81 (P = .01), I^2 = 68.8\%

Test for overall effect: \(Z = 1.86 (P = .06)\)
Meta-analysis: Long-term Antidepressant Adjunct vs. Placebo in BP

Risk of New Depression

Meta-analysis: Affective Switch With Antidepressant vs. Placebo in BP

Studies were 16 weeks or less.

Meta-analysis: Long-term Antidepressant Adjunct vs. Placebo in BP

Risk of New Mania

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

Psychotherapy With Positive Evidence (Adjunct)

• 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
Bipolar Depression: NEI Practice Guideline

Add-on Novel or Experimental Agents

1. Add modafinil, armodafinil, or pramipexole
2. Cautiously consider adding bupropion
3. Replace one or both agents with alternate first- or second-line agents
4. Consider ECT, third-line agents, and novel or experimental options

Stahl SM. CNS Spectrums; in press.
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Armodafinil in Bipolar Depression: Adjunct


**Response Rates**
- Armodafinil: 46.2%
- Placebo: 34.2%

**AE Discontinuation**
- Armodafinil: 5.6%
- Placebo: 3.5%

**≥7% Weight Gain**
- Armodafinil: 1.6%
- Placebo: 4.4%

Response: ≥50% decrease in IDS-C30
Pramipexole in Bipolar Depression: Adjunct

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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<td>Mood</td>
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<td>0</td>
<td>+</td>
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<td>Stabilizers</td>
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<td>Side</td>
<td>0</td>
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<td>++</td>
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<td>GL, acne, thyroid, renal</td>
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<td>Effects</td>
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<th>ASEN</th>
<th>CBZ</th>
<th>ILOP</th>
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<th>RSP</th>
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<td>oral hypoesthesia</td>
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<td>+</td>
<td>+++</td>
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<td>+</td>
<td>0</td>
<td>nausea, headache, rash</td>
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<td>nausea, rash</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>activation (low dose)</td>
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</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**

- Placebo (n=147): Median change from baseline = -3.0 mg/dL, BL Mean = 197.4 mg/dL
- Lurasidone 20-60 mg (n=140): Median change from baseline = 0.0 mg/dL, BL Mean = 196.0 mg/dL
- Lurasidone 80-120 mg (n=144): Median change from baseline = -3.0 mg/dL, BL Mean = 202.2 mg/dL

**Triglycerides**

- Placebo (n=147): Median change from baseline = 8.0 mg/dL, BL Mean = 125.2 mg/dL
- Lurasidone 20-60 mg (n=140): Median change from baseline = 3.0 mg/dL, BL Mean = 132.4 mg/dL
- Lurasidone 80-120 mg (n=144): Median change from baseline = -2.0 mg/dL, BL Mean = 133.9 mg/dL

Metabolic Changes With Lurasidone

## 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>
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<tbody>
<tr>
<td>Liver</td>
<td>D, C</td>
<td>C**</td>
<td>D***</td>
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<td>D, C</td>
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<tr>
<td>CBC</td>
<td>C</td>
<td>C**</td>
<td>D***</td>
<td>C, D</td>
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<tr>
<td>Menstrual change</td>
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<td>Calcium</td>
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<td>Serum levels*</td>
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<tr>
<td>Weight</td>
<td>D, A</td>
<td>A**</td>
<td>D***, A</td>
<td>L</td>
<td>L, D, A</td>
</tr>
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<td>BP</td>
<td>A</td>
<td></td>
<td>A***</td>
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<td>A</td>
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<td>Fasting lipids</td>
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<tr>
<td>Fasting glucose</td>
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<td></td>
<td></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
- aripiprazole
- valproate
- olanzapine
- quetiapine
- risperidone
- ziprasidone
- psychotherapy
- psychoeducation

Bipolar Maintenance: What Has Consistent Positive Evidence

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

*Injectable

Antipsychotics in Bipolar Maintenance

Number Needed to Treat (sig)

- **Any Episode**
- **Mania**
- **Depression**

- Ari (Keck 2007)
- Olz (Tohen 2006)
- Que adj (Vieta 2008)
- Que adj (Suppes 2009)
- Que (Weisler 2009)
- Ris LA (Quiroz 2010)
- Ris LA (MacFadden 2009)
- Zip adj (Bowden 2010)

Anticonvulsants and Lithium in Bipolar Maintenance

Bipolar Maintenance: What's Recommended

**BAP**
- lithium*
- lamotrigine**
- valproate*
- olanzapine*
- quetiapine

**CANMAT**
- lithium
- lamotrigine
- valproate
- olanzapine
- quetiapine
- risperidone***
- ziprasidone

**NICE**
- lithium
- valproate
- olanzapine

*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.
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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.
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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