Improving the Recognition and Treatment of Bipolar Depression

page 37 in syllabus

Andrew J. Cutler, MD

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University of Florida, Gainesville

CEO and Chief Medical Officer, Florida Clinical Research Center, LLC

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Additionally sponsored by Fairleigh Dickinson University School of Psychology

This activity is supported by educational grants from: Lilly USA, LLC; Otsuka America Pharmaceutical, Inc.; Pamlab, L.L.C.; Sunovion Pharmaceuticals Inc.; Takeda Pharmaceuticals International, Inc., U.S. Region and Lundbeck Pharmaceutical Services, LLC; Teva Pharmaceutical Industries Ltd.

with additional support from: Assurex Health, Inc.; JayMac Pharmaceuticals, LLC; Neuronetics, Inc. For further information concerning Lilly grant funding, visit www.lillygrantoffice.com.

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Individual Disclosure Statement

Faculty Editor/Presenter

Andrew J. Cutler, MD, is a courtesy assistant professor in the department of psychiatry at the University of Florida in Gainesville, and the CEO and chief medical officer of Florida Clinical Research Center, LLC in Bradenton.

Grant/Research: Abbott/AbbVie, Akili Interactive, Alkermes, Arbor, AstraZeneca, Euthymics/Neurovance, Forest, Genentech, Janssen, Lilly, Lundbeck, Merck, Methylation Sciences, Neos, Next Wave/Pfizer, Novartis, OptiNose, Otsuka America, Pamlab, Pfizer, Purdue, Quintiles, Rhodes, Shionogi, Shire, Sunovion, Supernus, Takeda, Targacept, Theravance, Vanda

Consultant/Advisor: Abbott/AbbVie, Akili Interactive, Alkermes, Arbor, AstraZeneca, Euthymics/Neurovance, Forest, Genentech, Janssen, Lilly, Lundbeck, Methylation Sciences, Mylan, Neos, Next Wave/Pfizer, Novartis, Noven, OptiNose, Otsuka America, Pamlab, Pfizer, Quintiles, Rhodes, Shionogi, Shire, Sunovion, Supernus, Takeda, Targacept, Theravance, Vanda

Speakers Bureau: AstraZeneca, Forest, Janssen, Lilly, Lundbeck, Novartis, Otsuka America, Pamlab, Pfizer, Shionogi, Shire, Sunovion, Takeda
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. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 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<0.05
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

## Bipolar II Disorder vs. Major Depressive Disorder

<table>
<thead>
<tr>
<th>Variables: mean (SD), %</th>
<th>BP-II ($n=389$)</th>
<th>MDD ($n=261$)</th>
<th>OR (95% CI)</th>
</tr>
</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>
</tr>
<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>
</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</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>
TREATMENT OF BIPOLAR DEPRESSION: EFFICACY
Depression-Minded Treatments

- Hypomania
  - Treat from below
  - Stabilize from below

- Depression
  - Treat from below
# Bipolar Depression: What's Available

<table>
<thead>
<tr>
<th>Blue</th>
<th>Carbamazepine</th>
<th>Lithium</th>
<th>Carbamazepine</th>
<th>Aripiprazole</th>
<th>Bupropion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyan</td>
<td>Lamotrigine</td>
<td></td>
<td>Lamotrigine</td>
<td>Asenapine</td>
<td>Fluoxetine</td>
</tr>
<tr>
<td>Cyan</td>
<td>Oxcarbazepine</td>
<td></td>
<td>Oxcarbazepine</td>
<td>Iloperidone</td>
<td>Paroxetine</td>
</tr>
<tr>
<td>Cyan</td>
<td>Valproate</td>
<td></td>
<td>Valproate</td>
<td>Lurasidone</td>
<td>Other ADs</td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td>Olanzapine</td>
<td></td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td>Paliperidone</td>
<td></td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td>Quetiapine</td>
<td></td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td>Risperidone</td>
<td></td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td>Ziprasidone</td>
<td></td>
</tr>
<tr>
<td>Cyan</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>OFC</td>
</tr>
</tbody>
</table>
Bipolar Depression: What's (Relatively) Well Studied

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

Bipolar Depression: What Has Consistent Positive Evidence

- lurasidone
- quetiapine

Quetiapine in Bipolar Depression

**MADRS WMD (95% CI)**

- **Calabrese et al. 2005**
  -6.47 (-8.67; -4.27)

- **Thase et al. 2006**
  -4.07 (-6.03; -2.11)

- **Young et al. 2010**
  -4.29 (-6.28; -2.3)

- **McElroy et al. 2010**
  -3.71 (-6.22; -1.2)

- **Quetiapine 600 pooled**
  -4.64 (-5.82; -3.46)

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**
  -5.51 (-7.88; -3.14)

- **Quetiapine 200 pooled**
  -4.76 (-5.75; -3.76)

Heterogeneity: Q=4.19; p=0.381

Overall: Z=-9.37; p=0; n=1661

Favors: QUET PBO
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.

Lurasidone in Bipolar Depression: Monotherapy

Change From Baseline in MADRS (MMRM)

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

Lurasidone in Bipolar Depression: Adjunct

Change From Baseline in MADRS (MMRM)

Placebo + Li/VPA (N=161)
Baseline mean = 30.8
Mean daily dose of lurasidone: 66.3 mg (90% of participants received ≥60 mg)

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

Effect size: 0.34 (MMRM)

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

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# 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>ADs</td>
<td></td>
<td>SSRIs, BUP (adj)</td>
<td>SSRIs (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

Not on medication
- Add VAL
- Add Li + VAL

Stahl SM. CNS Spectrums; in press.
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# 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.

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

Risk of New Depression

Pooled RR
(0.73 [0.55–0.97])

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

Pooled RR
(1.72 [1.23–2.41])

## Meta-analysis: Risk of Switch to Mania

<table>
<thead>
<tr>
<th>Measure</th>
<th>Contrast</th>
<th>Studies (n)</th>
<th>RR (95% CI)</th>
<th>z</th>
<th>P-value</th>
<th>NNH (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall meta-analysis</td>
<td>AD effect</td>
<td>48</td>
<td>1.76 (1.33-2.33)</td>
<td>3.94</td>
<td>&lt;0.0001</td>
<td>27.2 (16.7-75.3)</td>
</tr>
<tr>
<td>Trial design</td>
<td>RCT</td>
<td>30</td>
<td>1.43 (1.10-1.86)</td>
<td>2.66</td>
<td>&lt;0.008</td>
<td>28.7 (19.2-69.2)</td>
</tr>
<tr>
<td>Trial design</td>
<td>Open</td>
<td>18</td>
<td>1.95 (1.37-2.78)</td>
<td>3.71</td>
<td>&lt;0.0001</td>
<td>28.9 (13.8-∞)</td>
</tr>
<tr>
<td>Dx</td>
<td>BP</td>
<td>25</td>
<td>1.13 (0.90-1.42)</td>
<td>1.08</td>
<td>0.282</td>
<td>41.7 (18.5-∞)</td>
</tr>
<tr>
<td>Dx</td>
<td>MDD</td>
<td>22</td>
<td>3.76 (2.77-5.09)</td>
<td>8.56</td>
<td>&lt;0.0001</td>
<td>22.8 (13.2-85.4)</td>
</tr>
<tr>
<td>AD type</td>
<td>MAOI</td>
<td>6</td>
<td>2.83 (0.79-10.2)</td>
<td>1.60</td>
<td>0.110</td>
<td>31.3 (14.6-∞)</td>
</tr>
<tr>
<td>AD type</td>
<td>TCA</td>
<td>30</td>
<td>1.93 (1.13-3.30)</td>
<td>2.41</td>
<td>0.016</td>
<td>18.5 (8.65-∞)</td>
</tr>
<tr>
<td>AD type</td>
<td>SRI+SNRI</td>
<td>9</td>
<td>1.70 (0.87-3.32)</td>
<td>1.56</td>
<td>0.119</td>
<td>90.9 (16.9-∞)</td>
</tr>
<tr>
<td>MS</td>
<td>Without</td>
<td>33</td>
<td>1.76 (1.27-2.44)</td>
<td>3.41</td>
<td>0.001</td>
<td>58.7 (37.9-131)</td>
</tr>
<tr>
<td>MS</td>
<td>With</td>
<td>15</td>
<td>1.73 (1.18-2.54)</td>
<td>2.81</td>
<td>0.005</td>
<td>27.2 (15.3-125)</td>
</tr>
</tbody>
</table>
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

Lolich M. Actas Esp Psiquiatr 2012;40(2):84-92;
Bipolar Depression: NEI Practice Guideline

Add-on Novel or Experimental Agents

- 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

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Armodafinil in Bipolar Depression: Adjunct

Response Rates

<table>
<thead>
<tr>
<th>armodafinil</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>46.2%</td>
<td>34.2%</td>
</tr>
</tbody>
</table>

AE Discontinuation

<table>
<thead>
<tr>
<th>armodafinil</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.6%</td>
<td>3.5%</td>
</tr>
</tbody>
</table>

≥7% Weight Gain

<table>
<thead>
<tr>
<th>armodafinil</th>
<th>placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6%</td>
<td>4.4%</td>
</tr>
</tbody>
</table>

Response: ≥50% decrease in IDS-C30

Pramipexole in Bipolar Depression: Adjunct

TREATMENT OF BIPOLAR DEPRESSION: SAFETY AND TOLERABILITY
## Mood Stabilizers: Side Effects

<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>0</td>
<td>0</td>
<td>0</td>
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</tr>
<tr>
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<td>0</td>
<td>++</td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>++</td>
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<tr>
<td></td>
<td>0</td>
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<td>++</td>
<td>+++</td>
<td>++</td>
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<td></td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>tremor, GI</td>
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</table>


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

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

### Metabolic Changes With Lurasidone

<table>
<thead>
<tr>
<th>Safety Population</th>
<th>Cholesterol</th>
<th>Triglycerides</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Placebo</strong> (n=147)</td>
<td>Median Change From Baseline (mg/dL)</td>
<td>Median Change From Baseline (mg/dL)</td>
</tr>
<tr>
<td>BL Mean: 197.4 mg/dL</td>
<td>-3.0</td>
<td>8.0</td>
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<tr>
<td>Lurasidone 20-60 mg (n=140) Median Change From Baseline (mg/dL)</td>
<td>0.0</td>
<td>3.0</td>
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<tr>
<td>196.0 mg/dL</td>
<td>202.2 mg/dL</td>
<td>125.2 mg/dL</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=144) Median Change From Baseline (mg/dL)</td>
<td>-3.0</td>
<td>-2.0</td>
</tr>
<tr>
<td>202.2 mg/dL</td>
<td>132.4 mg/dL</td>
<td>133.9 mg/dL</td>
</tr>
</tbody>
</table>


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Metabolic Changes With Lurasidone

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# Mood Stabilizers: Side Effects (cont.)

<table>
<thead>
<tr>
<th></th>
<th>ARIP</th>
<th>ASEN</th>
<th>CBZ</th>
<th>ILOP</th>
<th>OXC</th>
<th>PAL</th>
<th>RSP</th>
<th>ZIP</th>
<th>Other</th>
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<td>+</td>
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<td>+</td>
<td>+</td>
<td>nausea</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>+</td>
<td>nausea, headache, rash</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>0</td>
<td>0</td>
<td>nausea, rash</td>
</tr>
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<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>+</td>
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<td>++</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>activation (low dose)</td>
</tr>
</tbody>
</table>

---

# 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>
<td>D, C</td>
<td></td>
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<tr>
<td>Renal</td>
<td>L</td>
<td>C**</td>
<td>L</td>
<td>C</td>
<td></td>
</tr>
<tr>
<td>TSH</td>
<td></td>
<td></td>
<td>L</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>CBC</td>
<td>C</td>
<td>C**</td>
<td>D***</td>
<td>C, D</td>
<td></td>
</tr>
<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>L</td>
<td>L</td>
<td></td>
</tr>
<tr>
<td>Serum levels*</td>
<td></td>
<td></td>
<td>L</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>A***</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Fasting lipids</td>
<td>A</td>
<td></td>
<td>A</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>A</td>
<td></td>
<td>A</td>
<td>A</td>
<td></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
- psychotherapy
- psychoeducation
- OFC
Bipolar Maintenance: What's (Relatively) Well Studied

- Lithium
- Carbamazepine
- Aripiprazole
- Psychotherapy
- Lamotrigine
- Psychoeducation
- Valproate
- Olanzapine
- Quetiapine
- Risperidone
- Ziprasidone

Bipolar Maintenance: What Has Consistent Positive Evidence

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

*Injectable

Antipsychotics in Bipolar Maintenance

Number Needed to Treat (sig)

- 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

Number Needed to Treat (sig)

- Any Episode
- Mania
- Depression

Lam (Bowden 2003)
Lam (Calabrese 2000)
Li (Prien 1973)
Li (Goodwin 2004)
Li (Bowden 2003)
Li (Weisler 2009)
Val (Bowden 2000)

Bipolar Maintenance: What's Recommended

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

**CANMAT**
- lithium
- lamotrigine
- valproate
- aripiprazole*
- 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>
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<tr>
<td>Oxcarbazepine</td>
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</tr>
<tr>
<td>Quetiapine</td>
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<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 ilurasidone

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

• Patient and family education are integral, particularly for being vigilant for and addressing prodromal symptoms
Post-Poll Question

I feel competent managing patients with bipolar depression.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 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