Handout for the Neuroscience Education Institute (NEI) online activity:

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
DIFFERENTIAL DIAGNOSIS
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</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

"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
Bipolar Depression: What Has Consistent Positive Evidence

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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</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>ADs</td>
<td></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 + VAL

Not on medication
  - Add VAL
  - Add Li + VAL

Stahl SM. CNS Spectrums; in press.
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)

• 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;
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.
BIPOLAR MAINTENANCE
Bipolar Maintenance: What Has Consistent Positive Evidence

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

*Injectable

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>
<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.
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 for being vigilant for and addressing prodromal symptoms.