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

Bipolar Depression: Misdiagnosis Leads to Mistreatment
Learning Objectives

• Apply evidence-based strategies to differentially diagnose patients presenting in depressive states

• Apply evidence-based treatment strategies to the management of patients with bipolar disorder

• Optimize treatment for bipolar disorder based on the long-term needs of the patient
Pre-Poll Question 1

I feel competent diagnosing patients with bipolar depression.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Pre-Poll Question 2

I feel competent **optimizing treatment** for patients with bipolar depression.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
A 28-year-old obese 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 agent with the lowest risk of cardiometabolic side effects is:

1. Lithium
2. Lurasidone
3. Valproate
Pretest Question 2

Janet is a 43-year-old patient with bipolar disorder. She is currently depressed with some features of hypomania. Practice guidelines recommend treatment with an antidepressant in patients with bipolar disorder under the following conditions:

1. As adjunct for acute bipolar I or II depressive episode with ≥2 concomitant manic symptoms, psychomotor agitation, or rapid cycling
2. During manic and depressive episodes with mixed features
3. In patients with predominantly mixed states
4. All of the above
5. None of the above
DIFFERENTIAL DIAGNOSIS
We Can Do Better

• Correct diagnosis of BP within the first year of symptom onset is made in only 20% of cases
• Average time between onset of BP symptoms and first appropriate treatment = 10 years
• Undiagnosed BP = 49%
• Misdiagnosed BP = As high as 60%
• 78% of PCPs fail to detect or misdiagnose BP
• Up to 12.5% of individuals diagnosed with MDD will experience a manic or hypomanic episode over an 11-year period

Why Is An Early, Accurate Diagnosis Important?

- Consequences of not identifying bipolar depression early:
  - Worse quality of life
  - Inaccurate and potentially harmful treatment
  - Increased cycling and risk of relapse
  - Reduced treatment response (e.g., lithium)
  - Increased risk of suicide
  - Increased subsequent morbidity
  - High economic costs

Increased Risk of Cycling and Relapse

Suicide

- 29% of patients with BD attempt suicide at least once in their life
- 10–20% of patients with BD take their own life
- Suicide rates are 20X higher for BD compared to the general population
- Suicide rates are 2X higher for BD compared to MDD

Risk of Suicide Attempt Depends On Mood Phase

### Clinical Characteristics and Implications of Polarity Categorization

<table>
<thead>
<tr>
<th>Depressed</th>
<th>Mixed</th>
<th>Manic</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Predominantly Depressed</strong></td>
<td><strong>Predominantly Depressed + Mixed</strong></td>
<td><strong>Predominantly Manic + Mixed</strong></td>
</tr>
<tr>
<td>• 2X higher risk of suicide</td>
<td>• 4X higher risk of suicide</td>
<td>• 1.28 higher risk of drug abuse</td>
</tr>
<tr>
<td>• 2X higher risk of Axis-II comorbidity</td>
<td>• 3X higher risk of Axis-II comorbidity</td>
<td>• Manic or psychotic 1st episode</td>
</tr>
<tr>
<td>• Depressive or mixed 1st episode</td>
<td>• Depressive or mixed 1st episode</td>
<td>• 12 years or more of education</td>
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<tr>
<td>• Longer duration to diagnosis</td>
<td>• Longer duration to diagnosis</td>
<td>• Family history of an affective illness</td>
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<td>• Female</td>
<td>• Female</td>
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<tr>
<td>• Ever in a mixed state</td>
<td>• Ever in a mixed state</td>
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<tr>
<td>• Ever married</td>
<td>• Ever married</td>
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</tr>
<tr>
<td>• Ever received ECT</td>
<td>• Ever received ECT</td>
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</table>

**Clinical Characteristics**
*(at least 25% more prevalent compared to opposite pole)*

Diagnostic Conversion From MDD to BD

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

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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 include:
    - Irritability, mental overactivity, psychomotor agitation, talkativeness
  - Individuals with subthreshold hypomania have a more severe illness course

- High impulsivity increases the rate of conversion

- BPII versus MDD: distinct disorders or continuity on the mood spectrum?

Progression to Bipolar Disorder In Patients With 3+ Hypomanic Symptoms

Why Is Making An Early and Accurate Diagnosis of Bipolar Depression So Difficult?

- Most patients present when depressed
- Hypomania is often pleasant for patients and may not be mentioned
- Strict diagnostic criteria in DSM-IV
  - DSM-5 now recognizes the importance of changes in activity as well as mood
  - Mixed specifiers now acknowledge depression with hypomanic features as well as hypomania with depressive features
- Mania is often atypical (especially in youth) with irritability and flight of ideas rather than euphoria and grandiosity

Long-term Symptomatic Status of Patients With Bipolar II Disorder

Finding a Needle In the Haystack…

What you must search for

- Euthymic: 46%
- Depressed: 50%
- Hypomanic: 2%
- Cycling/Mixed: 2%

How patients typically present

THE PROBABILISTIC APPROACH TO DIFFERENTIAL DIAGNOSIS

Beyond Symptoms of Mania/Hypomania:
More Common In Bipolar Depression

- Irritability
- Feelings of guilt
- More previous depressive episodes
- History of suicide attempts
- Morning worsening of symptoms
- Catatonic features
- Comorbid substance use disorder
- Hypersomnia
- Earlier age of onset (<25 years)
- Early morning insomnia
- Psychomotor retardation (BP-I)
- Shorter depressive episodes
- Psychomotor agitation (BP-II)
- Comorbid personality disorder
- Overeating/weight gain
- Family history of substance abuse
- Restlessness
- Melancholic features
- Family history of BP
- More previous depressive episodes
- History of suicide attempts
- Morning worsening of symptoms

Melancholic features
Family history of BP
Comorbid personality disorder
Early age of onset (<25 years)
More previous depressive episodes
Catatonic features
Morning worsening of symptoms
Family history of substance abuse
Psychomotor retardation (BP-I)
Feelings of guilt
Irritability
Restlessness

UNIPOLAR DEPRESSION
Comorbid substance use disorder
Psychomotor agitation (BP-II)
Hypersomnia
Shorter depressive episodes
Psychotic symptoms
History of suicide attempts
Overeating/weight gain
Mood reactivity
Early morning insomnia

BIPOLAR DEPRESSION

The Probabilistic Approach: Diagnostic Guidelines

<table>
<thead>
<tr>
<th>Suspect Bipolar Depression If 5+ Are Present:</th>
<th>Suspect Unipolar Depression If 4+ Are Present:</th>
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</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>Psychotic features and/or pathological guilt</td>
<td></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>

Potential Caveats to the Probabilistic Approach: Psychomotor Disturbance

• Some studies find **psychomotor retardation** more common in bipolar depression than unipolar depression, other studies do not

• Some studies find **psychomotor agitation** more common in bipolar depression than unipolar depression, other studies do not

• Psychomotor retardation may be more indicative of BP-I

• Psychomotor agitation may be more indicative of BP-II

Potential Caveats to the Probabilistic Approach: Sleep Disturbance

• Some studies have found that patients with BP depression have hypersomnia, whereas patients with MDD have initial insomnia and reduced sleep

• One recent study in women showed:
  – Patients with MDD reported either insomnia or hypersomnia
  – Patients with BP II complained of both insomnia and hypersomnia

Family History

- Although the majority of patients with BP depression do not have a family history of BP, family history of BP is arguably the most robust and reliable risk factor for BP depression.
- Individuals with a first-degree relative with BP disorder are at an 8X greater risk of developing BP disorder compared to the general population.
- The importance of questioning depressed patients about family history of affective disorders cannot be overemphasized.

Bipolar Depression Rating Scale (BDRS)

- Clinician administered 20–item scale including 3 subscales
  - Psychological Depression
    - Anxiety, guilt, suicidality, worthlessness, irritability, etc
  - Somatic depression
    - Sleep disturbance, energy reduction, reduced concentration, etc
  - Mixed
    - Psychotic symptoms, lability, increased speech, etc

<table>
<thead>
<tr>
<th>32-Item Hypomania Checklist (HCL-32)</th>
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</thead>
<tbody>
<tr>
<td>I need less sleep</td>
</tr>
<tr>
<td>I feel more energetic and more active</td>
</tr>
<tr>
<td>I am more self-confident</td>
</tr>
<tr>
<td>I enjoy my work more</td>
</tr>
<tr>
<td>I am more sociable (make more phone calls, go out more)</td>
</tr>
<tr>
<td>I want to travel and/or do travel more</td>
</tr>
<tr>
<td>I tend to drive faster or take more risks when driving</td>
</tr>
<tr>
<td>I spend more money/too much money</td>
</tr>
<tr>
<td>I take more risks in my daily life (in my work and/or other activities)</td>
</tr>
<tr>
<td>I am physically more active (sport, etc)</td>
</tr>
<tr>
<td>I plan more activities or projects</td>
</tr>
<tr>
<td>I have more ideas, I am more creative</td>
</tr>
<tr>
<td>I am less shy or inhibited</td>
</tr>
<tr>
<td>I wear more colorful and more extravagant clothes/make-up</td>
</tr>
<tr>
<td>I want to meet or actually do meet more people</td>
</tr>
<tr>
<td>I am more interested in sex, and/or have increased sexual desire</td>
</tr>
<tr>
<td>15-Item Hypomania Checklist (HCL-15)</td>
</tr>
<tr>
<td>-------------------------------------</td>
</tr>
<tr>
<td>Less sleep</td>
</tr>
<tr>
<td>More drive or energy</td>
</tr>
<tr>
<td>More self-confidence</td>
</tr>
<tr>
<td>Increased social activity and work motivation</td>
</tr>
<tr>
<td>Increased physical activity</td>
</tr>
<tr>
<td>More plans and ideas</td>
</tr>
<tr>
<td>Less shy, less inhibited</td>
</tr>
<tr>
<td>More talkative than usual</td>
</tr>
<tr>
<td>More puns and jokes, faster thinking, laughing more</td>
</tr>
<tr>
<td>More irritable, impatient</td>
</tr>
<tr>
<td>Increased consumption of coffee, cigarettes</td>
</tr>
<tr>
<td>Increased consumption of alcohol</td>
</tr>
<tr>
<td>Extremely happy mood, overeuphoric</td>
</tr>
<tr>
<td>Increased sex drive, interest in sex</td>
</tr>
<tr>
<td>Over-activity (e.g., shopping, business, telephone calls, travelling, visiting people)</td>
</tr>
</tbody>
</table>

A depressed patient who endorses less than 7 items has a 93% likelihood of having MDD rather than BPII.

Mood Disorders Questionnaire (MDQ)

- 13 yes/no self-report answers
- Screens for lifetime history of manic/hypomaniac symptoms
- Shorter and possibly more accurate than the HCL-32
- However, the HCL may be better for detecting subthreshold hypomania symptoms

Mood Swings Questionnaire (MSQ)

• Score of 22 or more warrants detailed clinical assessment

• Available as an anonymous online self-test at: www.blackdoginstitute.org.au

• 35% of patients who consulted a health care professional following an online MSQ positive screen had a diagnosis of BP confirmed

• Superior sensitivity and specificity compared to the MDQ

TREATMENT OF BIPOLAR DEPRESSION: EFFICACY
Quetiapine in Bipolar Depression

Study
Calabrese et al. 2005
Thase et al. 2006
Young et al. 2010
McElroy et al. 2010
Quetiapine 600 pooled

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)

Heterogeneity: Q=3.64; p=0.303
Overall: Z=-7.71; p=0; n=1396

Calabrese et al. 2005
Thase et al. 2006
Young et al. 2010
McElroy et al. 2010
Suppes et al. 2010
Quetiapine 200 pooled

MADRS WMD (95% CI)
-6.13 (-8.33; -3.93)
-5.01 (-6.95; -3.07)
-3.55 (-5.55; -1.55)
-3.59 (-6.1; -1.08)
-5.51 (-7.88; -3.14)
-4.76 (-5.75; -3.76)

Heterogeneity: Q=4.19; p=0.381
Overall: Z=-9.37; p=0; n=1661

Favors: QUET PBO

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

<table>
<thead>
<tr>
<th>Treatment</th>
<th>LS Mean Change from Baseline</th>
<th>Effect size (MMRM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=162)</td>
<td>Baseline mean = 30.5</td>
<td></td>
</tr>
<tr>
<td>Lurasidone 20–60 mg (n=161)</td>
<td>Baseline mean = 30.3</td>
<td>0.51</td>
</tr>
<tr>
<td>Lurasidone 80–120 mg (n=162)</td>
<td>Baseline mean = 30.6</td>
<td>0.51</td>
</tr>
</tbody>
</table>

*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)

*\(p<0.05\)  **\(p<0.01\)  ***\(p<0.001\)

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

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

Bipolar Depression: NEI Practice Guideline

## Recommended Doses in Bipolar Depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>Daily dose</th>
<th>Drug</th>
<th>Daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>lamotrigine (mono)</td>
<td>100–200 mg</td>
<td>aripiprazole</td>
<td>15–30 mg (maint)</td>
</tr>
<tr>
<td>lithium</td>
<td>0.6–1.0 mEq/L</td>
<td>asenapine</td>
<td>5–10 mg (maint)</td>
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<tr>
<td>lurasidone</td>
<td>20–120 mg</td>
<td>carbamazepine</td>
<td>4–15 mg/L (maint)</td>
</tr>
<tr>
<td>olanzapine-fluoxetine</td>
<td>6–12/25–50 mg</td>
<td>iloperidone</td>
<td>12–24 mg (maint)</td>
</tr>
<tr>
<td>quetiapine</td>
<td>300 mg</td>
<td>oxcarbazepine</td>
<td>1200–2400 mg (mania)</td>
</tr>
<tr>
<td>valproate</td>
<td>70–90 mg/L</td>
<td>paliperidone</td>
<td>6 mg (schiz)</td>
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<tr>
<td></td>
<td></td>
<td>risperidone</td>
<td>25–50 mg IM q2wks (maint)</td>
</tr>
<tr>
<td></td>
<td></td>
<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 symptoms, psychomotor agitation, or rapid cycling
  - As monotherapy in bipolar I disorder
  - As monotherapy in bipolar II depression with ≥2 concomitant manic symptoms
  - 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
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 150 mg

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

Armodafinil in Bipolar Depression: Adjunct

Response: ≥50% decrease in IDS-C30

Pramipexole in Bipolar Depression: Adjunct

Omega-3 Fatty Acids

• Principal dietary sources include fatty cold water fish and fish oil supplements
• Increased fish intake is associated with reduced lifetime prevalence of mood disorders
• 1-4 g/day omega-3 supplementation may:
  – Reduce manic and depressive symptom severity
  – Reduce BP relapse rates
  – Reduce risk of suicide
  – Protect against adverse cardiometabolic effects
  – Has little safety risk

Why Treat Bipolar Disorder With Psychotherapy?

- Increase adherence to medication
- Enhance social and occupational functioning
- Enhance capacity to manage stressors in the social-occupational milieu
- Enhance protective effects of family and other social supports
- Decrease denial and trauma and encourage acceptance of the disorder
- Decrease the risk of recurrence

Empirically Tested Psychotherapies for Bipolar Disorder

- Cognitive Behavioral Therapy (CBT)
- Psychoeducation (Group)
- Psychoeducation (Individual)
- Family Focused Therapy (FFT)
- Interpersonal and Social Rhythm Therapy (IPSRT)

TREATMENT OF BIPOLAR DEPRESSION: SAFETY AND TOLERABILITY
Metabolic Syndrome and Obesity in Bipolar Disorder

• 68% of BP patients are overweight
• 32% of BP patients meet criteria for obesity (relative to < 20% of controls)
• Patients with BP are 3X more likely to have metabolic syndrome compared to healthy controls
  – Despite consuming fewer calories, carbohydrates, fats, and more fiber than healthy controls!
• Thus, although diet and lifestyle are factors, the story is much more complicated
  – Effects of pharmacological agents?
  – Common etiology of metabolic syndrome and BP?

Obesity May Predict Bipolarity in Depressed Patients

Obesity Decreases Time to Depressive Recurrence

Obese patients had a shorter time to depressive recurrence than non-obese patients

Cardiovascular Disease and Hypertension Among Adults With Bipolar I Disorder

### 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>
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<td>tremor, GI</td>
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</table>

Stahl SM. Stahl's essential psychopharmacology: the prescriber's guide. 4th ed. 2011;
Stahl SM. CNS Spectrums; in press.
## Mood Stabilizers: Side Effects (cont.)

<table>
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<tr>
<th></th>
<th>ARIP</th>
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<td>+</td>
<td>0</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)

- Olanzapine
- Quetiapine

Aripiprazole
Clozapine
Quetiapine
Risperidone
Ziprasidone

Olanzapine
Risperidone
Ziprasidone

FAVORS
FAVORS

Metabolic Changes With Lurasidone

**Cholesterol**

- Placebo (n=147): BL Mean 197.4 mg/dL, Median Change -3.0 mg/dL
- Lurasidone 20–60 mg (n=140): Median Change 0.0 mg/dL
- Lurasidone 80–120 mg (n=144): Median Change -3.0 mg/dL

**Triglycerides**

- Placebo (n=147): BL Mean 125.2 mg/dL, Median Change 8.0 mg/dL
- Lurasidone 20–60 mg (n=140): Median Change 3.0 mg/dL
- Lurasidone 80–120 mg (n=144): Median Change 133.9 mg/dL

Safety Population

**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>
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<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>L</td>
<td>L</td>
<td>L</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>L</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>A</td>
</tr>
<tr>
<td>Fasting glucose</td>
<td>A</td>
<td></td>
<td>A</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


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BIPOLAR MAINTENANCE
Major Goals of Treatment in Bipolar Disorder

- Prevent future episodes of mania
- Prevent mixed episodes
- Prevent episodes of depression
- Diminish the presence of subsyndromal depression over extended periods of time
- Improve functioning
- Decrease morbidity and mortality
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

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.
## Summary: Assessment and Treatment of Interepisodic Symptom Domains

<table>
<thead>
<tr>
<th>Domain</th>
<th>Assessment</th>
<th>Treatment</th>
</tr>
</thead>
</table>
| Abnormal emotional reactivity | - Affective Lability Scale  
- Affect Intensity Measure         | - Stress management  
- Relaxation  
- Treatment to be developed      |
| Sleep and circadian rhythm disturbances | - Sleep diary  
- Pittsburgh Sleep Quality Index | - Psychoeducation  
- Interpersonal and social rhythm therapy |
| Cognitive impairment          | - Neuropsychological assessment                                             | - Cognitive behavioral therapy  
- Cognitive remediation           |
| Psychiatric and medical comorbidities | - Psychiatric assessment  
- Risk factor assessment (Weight, BMI, hypertension, glucose tolerance, lipids, C-reactive protein) | - Treatment of comorbid psychiatric and medical disorders  
- Diet, exercise, and smoking cessation… |

Patient follow-up is pivotal; also important to consider benefit-risk profile of current or planned psychotropic medication

BMI, body mass index

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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Treatment Nonadherence

• As many as 77% of patients with BP may be intentionally or unintentionally nonadherent

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

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

Summary

• Standard depression rating scales do not differentiate between bipolar and unipolar depression

• It is essential that all patients presenting with depression are carefully screened for symptoms and risk factors associated with bipolar disorder

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

• Patient and family psychosocial interventions are integral, particularly for being vigilant for and addressing prodromal symptoms, as well as improving treatment adherence