BIPOLAR DISORDER: A SPECTRUM DISORDER WITH A SPECTRUM OF TREATMENTS

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Learning Objectives

• Review the spectrum of mood presentations seen in bipolar disorder (BP)

• Improve the diagnosis of both bipolar depression and bipolar mania

• Optimize treatment of both depression and mania in the context of BP
Although categorical classifications may be useful for clinical practice, the overwhelming majority of the evidence points to a dimensional (spectrum) view of mood disorders.

- e.g., treatment response (antidepressant vs. mood stabilizing agent) and links with family history of bipolar disorder.
Bipolar Disorder (BP) Mood Presentations

BP I
Manic or Mixed Episode ± Major Depressive Episode

BP II
Depressive and Hypomanic Episodes

### The Bipolar Spectrum

| ¼  | Depressive episodes but rapid poop out to antidepressant |
| ½  | Positive symptoms of psychosis with manic, hypomanic, and depressive episodes (i.e., schizobipolar disorder) |
| I  | **Manic or mixed episode ± major depressive disorder** |
| I½ | Protracted hypomania without depression |
| II | **Depressive and hypomanic episodes** |
| II½| Depressive episodes with cyclothymic temperament |
| III| Depressive episodes with antidepressant-induced hypomania |
| III½| Bipolar disorder with substance use |
| IV | Depressive episodes with hyperthymic temperament |
| V  | Depression with mixed hypomania |
| VI | Bipolarity in the setting of dementia |

Diagnosis of Bipolar Mania and Depression
Is It Bipolar Depression?

- Patients with BP typically seek help during depressive, not manic episodes (mixed features may be present)
- Clinicians will first be confronted with differentiating between unipolar and bipolar depression

Why is Making an Early and Accurate Diagnosis of Bipolar Depression So Difficult?

• 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 hypomaniac 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

Why is an Early, Accurate Diagnosis Important?

- Consequences of not identifying bipolar depression (BD) 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
- Overall mortality rate for BP is over 2.5 times higher than that of the general population

Higher Medical Comorbidity Burden in Women Than Men With Bipolar Disorder


* \( p \leq 0.01 \) Women > Men

^ \( p \leq 0.01 \) Men > Women

N=593,257

Are Medical Comorbid Conditions of Bipolar Disorder Due to Immune Dysfunction?

Medical Comorbidities With Immune Dysfunction Shown to Be Correlated With BP

- Guillain-Barre syndrome
- Crohn’s disease
- Autoimmune hepatitis
- Multiple sclerosis
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Psoriasis
- Autoimmune thyroiditis
- Obesity
- Type II diabetes mellitus
- Cardiovascular disease

Interaction of BP Diagnosis and Childhood Maltreatment Is Associated With Adult Morbidity

The interaction of bipolar diagnosis and childhood maltreatment type is associated with odds of having at least one medical illness in adulthood


The interaction of bipolar diagnosis and number of childhood maltreatment histories is associated with odds of having at least one medical illness in adulthood in a dose-dependent manner.

Suicide in BP

• 29% of patients with BP attempt suicide at least once in their life

• 10–20% of patients with BP take their own life

• Suicide mortality is 20x more likely for BP compared to the general population

• Suicide rates are twice as high for BP compared to major depressive disorder

Conus P et al. Bipolar Disord 2014;16(5):548-56;
Risk of Suicide Attempt Is Associated With Mood Polarity of BP

Incidence of suicide attempts in the Jorvi Bipolar Study 5-year follow-up for different polarity groups among sample of bipolar I (n=88) and bipolar II (n=100) disorder patients.

So You Think It’s Unipolar Depression?

• As many as 60% of patients with BP II are initially diagnosed as unipolar

• Correct diagnosis of bipolar disorder (BP) within the first year of symptom onset is made in only 20% of cases

• Over 1/3 of unipolar patients are eventually re-diagnosed as bipolar

• Average time between onset of BP symptoms and first appropriate treatment = 10 years

• Presence of even subthreshold (hypo)mania symptoms is strongly associated with conversion to bipolar disorder
  • Each (hypo)mania symptom increases risk by ~30%

Features More Common In Bipolar Than Unipolar Depression

- **Psychotic symptoms**
- **Psychomotor agitation (BP-II)**
- **History of suicide attempts**
- **Catatonic features**
- **Comorbid substance use disorder**
- **Early age of onset (<25)**
- **Hypersomnia**
- **Psychomotor retardation (BP-I)**
- **Overeating/weight gain**
- **Feelings of guilt**

- **Mood reactivity**
- **Restlessness**
- **Family history of substance abuse**
- **Melancholic features**
- **More prior depressive episodes (≥5)**
- **Irritability**
- **Morning worsening of symptoms**
- **Early morning insomnia**

References:
Neurobiological Marker Differentiates Unipolar From Bipolar Depression

VS activation in response to monetary reward is significantly blunted in unipolar depression (UD; n=33) and even more so in bipolar depression (BD; n=33), compared to healthy controls (HC; n=34).

Bipolar Depression Severity Is Associated With Diminished Neural Response to Social Rewards

Depression severity measured with Beck Depression Inventory (BDI) was inversely related to VS activation in response to social reward in bipolar depression (n=24), but not unipolar depression (n=24).

Family History

• Although the majority of patients with BD do not have a family history of BP, family history of BP is arguably the most robust and reliable risk factor for BD

• Individuals with a first-degree relative with BP are at an 8x greater risk of developing BP compared to the general population

• The importance of questioning depressed patients about family history of affective disorders can not be overemphasized

Detection of Subthreshold Hypomanic Symptoms

- Rapid Mood Screener (RMS)
- Bipolar Depression Rating Scale (BDRS)
- Hypomania Interview Guide (HIG)
- Mini International Neuropsychiatric Interview (M.I.N.I.)
- Clinically Useful Depression Outcome Scale with DSM-5 Mixed (CUDOS-M)
- Hypomania Checklist (HCL-32)
- Mood Disorder Questionnaire (MDQ)
- Altman Mania Rating Scale

See APPENDIX for more details on each assessment tool

One of the Most Important Questions to Ask Any Patient With Depression

Any manic/hypomanic symptoms and/or family history of bipolar disorder?

Every patient. Every time.
Treatment of Bipolar Mania and Depression
Mood Stabilizers

• No mood stabilizer is approved for use in bipolar depression
• There are some data demonstrating efficacy of lamotrigine for treating bipolar depression

Atypical Antipsychotics

<table>
<thead>
<tr>
<th>Medicine</th>
<th>FDA-approved for BP mixed states</th>
<th>FDA-approved for BP depression</th>
<th>FDA-approved for BP mania</th>
<th>FDA-approved for BP maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Asenapine</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Lurasidone</td>
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<td>✅</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>(with fluoxetine)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Quetiapine</td>
<td></td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Risperidone</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
<td>✅</td>
</tr>
</tbody>
</table>

What is the Role of Antidepressants?
Recommendations From the International Society for Bipolar Disorders (ISBD)

• When to avoid antidepressants:
  • 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 I or II depression with ≥2 concomitant manic symptoms
  • During manic and depressive episodes with mixed features
  • In patients with a history of past mania, hypomania, or mixed episodes emerging during antidepressant treatment
  • In patients with high mood instability (i.e., a high number of episodes) or with a history of rapid cycling
  • In patients with predominantly mixed states

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)

Metabolic Syndrome and Obesity in BP

- 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
  - BP daily intake of protein, carbohydrates, sugars, fiber, fats (all), and saturated fats is higher than 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?

Cardiovascular Disease (CVD) and Hypertension (HTN) Among Adults With Bipolar I Disorder

Bipolar > Depression > Control (p<0.001)

Odds Ratio (adjusting for age, sex, and race)

Control (n=34,851)
Depression (n=6,831)
Bipolar (n=1,411)
Obesity in Patients With Major Depressive Episode (MDE) Is Related to Bipolar and Mixed State Diagnostic Criteria

<table>
<thead>
<tr>
<th>MDE-Obese (n=493) &gt; MDE-Not Obese (n=2,291)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>DSM-IV Bipolar Disorder</strong></td>
</tr>
<tr>
<td>• DSM-IV Bipolar I ✓</td>
</tr>
<tr>
<td>• DSM-IV Bipolar II X</td>
</tr>
<tr>
<td><strong>Bipolar Specifier</strong></td>
</tr>
<tr>
<td>• Bipolar I specifier ✓</td>
</tr>
<tr>
<td>• Bipolar II specifier X</td>
</tr>
<tr>
<td><strong>Depressive Mixed State</strong></td>
</tr>
<tr>
<td>• DSM-5 criteria ✓</td>
</tr>
<tr>
<td>• RBDC mixed depression ✓</td>
</tr>
</tbody>
</table>

RBDC=Research-Based Diagnostic Criteria

The Association Between Depression and Arterial Stiffness Is Mediated by Metabolic Syndrome

Dregan A et al. JAMA Psychiatry 2020; e194712.

29% of the association of depression with arterial stiffness was mediated by metabolic syndrome.
## Mood Stabilizers: Side Effects

### All mood stabilizers used to treat bipolar mania cause weight gain

<table>
<thead>
<tr>
<th></th>
<th>Weight Gain</th>
<th>Sedation</th>
<th>Gastrointestinal Problems</th>
<th>Blurred Vision</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>+</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>headache, rash</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>headache, insomnia, rash</td>
</tr>
<tr>
<td>Lithium</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>tremor, acne, thyroid, renal, memory</td>
</tr>
<tr>
<td>Valproate</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>headache, tremor</td>
</tr>
</tbody>
</table>

### BP Atypical Antipsychotics: Side Effects

<table>
<thead>
<tr>
<th></th>
<th>Extrapyramidal Symptoms</th>
<th>Hyperprolactinemia</th>
<th>Weight Gain</th>
<th>Sedation</th>
<th>Hypotension</th>
<th>Gastrointestinal Problems</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>insomnia, headache</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>+</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>oral hypoesthesia</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Lurasidone</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Olanzapine</td>
<td>+</td>
<td>+</td>
<td>+++</td>
<td>++</td>
<td>+</td>
<td>++</td>
<td>dry mouth, pain</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+++</td>
<td>+</td>
<td>++</td>
<td>dry mouth</td>
</tr>
<tr>
<td>Risperidone</td>
<td>++</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+</td>
<td>0</td>
<td>insomnia, anxiety, sexual dysfunction</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>activation (low dose), dry mouth</td>
</tr>
</tbody>
</table>

**Most atypical antipsychotics used to treat bipolar mania and/or depression cause weight gain**

Treatment of Acute Bipolar Mania

**Level 1A**
- **MILD TO MODERATE**
  - Lithium
  - Aripiprazole, asenapine, divalproex, quetiapine, risperidone, ziprasidone, or cariprazine
- **SEVERE**
  - Lithium or divalproex + aripiprazole, asenapine, quetiapine or risperidone
  - Electroconvulsive therapy

**Level 1B**
- **MILD TO MODERATE**
  - Haloperidol or olanzapine

**Level 2**
- **MILD TO MODERATE**
  - Lithium + divalproex
  - Lithium and/or divalproex + 2nd generation antipsychotic (except clozapine)
  - Carbamezepine

**Level 3**
- Electroconvulsive therapy
- Clozapine + lithium or divalproex
- Lithium + carbamezepine
- Divalproex + carbamezepine

**Level 4**
- 3-drug combination of Level 1, 2, and 3 drugs (not 2 antipsychotics)

Selection of treatment should take maintenance treatment into account

2019-2020 Florida Best Practice Psychotherapy Medication Guidelines for Adults
Selection of treatment should take maintenance treatment into account.
Treatment of Continuation/Maintenance Therapy

Level 1
- Lithium
- Quetiapine
- Lamotrigine
- Maintain divalproex if initially stabilized
- Oral or LAI aripiprazole or LAI risperidone
- Quetiapine or ziprasidone adjunctive to lithium or divalproex
- Asenapine
- Manual-based psychotherapy

Level 2A
- Olanzapine
- Olanzapine adjunctive to lithium or divalproex

Level 2B
- Lithium + divalproex

Level 3
- Adjunctive clozapine (avoid combining with another antipsychotic)
- Electroconvulsive therapy

2019-2020 Florida Best Practice Psychotherapy Medication Guidelines for Adults
Summary

• A dimensional (spectrum) view of mood disorders may guide treatment more appropriately

• Unipolar and bipolar depression present with symptoms that are similar

• There are several probabilistic factors that may tip the scale towards a BP diagnosis

• Screening for (hypo)mania and asking about family history of BP is critical to making the differential diagnosis

• There are several treatment options for bipolar depression and mania available with varying metabolic tolerability profiles
A 17-year-old patient presents with symptoms of depression. He has always been a good student and a caring and responsible brother to his two younger siblings. Recently, however, he has become somewhat withdrawn and reports feeling sad much of the time. His MADRS score is 29, indicating moderate depression.

Given this information, what would be your most likely diagnosis for this patient?

1. Unipolar depression
2. Bipolar depression
3. I have not been given enough information to make an informed diagnosis
Posttest 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 $\geq 2$ 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
Arnold is a 24-year-old patient with bipolar mania. He also suffers from obesity. Based on existing controlled data, which of the following pharmacotherapies has the most evidence for avoiding as a first-line of treatment?

1. Carbamazepine
2. Aripiprazole
3. Quetiapine
4. Ziprasidone