BIPOLAR DISORDER: A SPECTRUM DISORDER WITH A SPECTRUM OF TREATMENTS
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
The Mood Disorder Spectrum

- 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

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

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 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

Conus P et al. Bipolar Disord 2014;16(5):548-56;
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≤0.01 Women>Men
- *p≤0.01 Men> Women

N=593,257

Medical Comorbidities
- 3x Greater Odds in Women than Men

Psychiatric Comorbidities
- 2.25x Greater Odds in Women than Men
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.


**Manic polarity**
\[\frac{2}{3}\] past episodes (hypo)manic (including mixed phases)

**Depressive polarity**
\[\frac{2}{3}\] past episodes depressive (including depressive mixed phases)

**No polarity**
~Equal # past episodes (hypo)manic and depressive

*\[p \leq 0.001\] greater than manic polarity group
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)
- Shorter depressive episodes
- Catatonic features
- Comorbid substance use disorder
- Hypersomnia
- Psychomotor retardation (BP-I)
- Overeating/weight gain
- Feelings of guilt

Mood reactivity

- Restlessness
- Family history of substance abuse
- More prior depressive episodes (≥5)
- Irritability

Melancholic features

- History of suicide attempts
- Family history of BP
- Early age of onset (<25)
- Morning worsening of symptoms
- Early morning insomnia

More prior depressive episodes (≥5)

- History of suicide attempts
- Family history of BP
- Early age of onset (<25)
- Morning worsening of symptoms
- Early morning insomnia

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).

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/hypomaniac 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

<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>Carbamazepine</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td></td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Lithium</td>
<td></td>
<td>✔</td>
<td>✔</td>
<td></td>
</tr>
<tr>
<td>Valproate</td>
<td>✔</td>
<td></td>
<td>✔</td>
<td></td>
</tr>
</tbody>
</table>

# Atypical Antipsychotics

<table>
<thead>
<tr>
<th></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>
<td></td>
<td>✓</td>
<td></td>
<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)

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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?

Bly MJ et al. Bipolar Disord 2014;16(3):277-88;
Cardiovascular Disease (CVD) and Hypertension (HTN) Among Adults With Bipolar I Disorder

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

- **Control** (n=34,851)
- **Depression** (n=6,831)
- **Bipolar** (n=1,411)

Bipolar > Depression > Control (p<0.001)

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>

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

29% of the association of depression with arterial stiffness was mediated by metabolic syndrome

Dregan A et al. JAMA Psychiatry 2020; e194712.
<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>

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

Selection of treatment should take maintenance treatment into account

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

- Lithium + divalproex
- Lithium and/or divalproex + 2nd generation antipsychotic (except clozapine)
- Carbamezapine

Level 3

- Electroconvulsive therapy
- Clozapine + lithium or divalproex
- Lithium + carbamezapine
- Divalproex + carbamezapine

Level 4

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

2019-2020 Florida Best Practice Psychotherapy Medication Guidelines for Adults
Treatment of Acute Bipolar Depression

**Level 1**
- ▲ Lurasidone or cariprazine
- ▲ Lamotrigine
- ▲ Quetiapine (for BP II)
- ▲ Lithium
- ▲ Lurasidone or lamotrigine adjunctive to lithium or divalproex
- ▲ NOT conventional antidepressants

**Level 2**
- ▲ Divalproex + lurasidone
- ▲ Olanzapine + fluoxetine (for BP I)
- ▲ 2-drug combinations of Level 1 drugs (but not 2 antipsychotics)

**Level 3**
- ▲ Electroconvulsive therapy

**Level 4**
- ▲ IV racemic ketamine and/or esketamine
- ▲ FDA-approved agent for BP + conventional antidepressant
- ▲ Pramipexole
- ▲ Adjunctive: modafinil, thyroid hormone (T3) or stimulants
- ▲ 3-drug combination
- ▲ TMS

Selection of treatment should take maintenance treatment into account

2019-2020 Florida Best Practice Psychotherapy Medication Guidelines for Adults
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

Treatment of Continuation/Maintenance 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
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
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
APPENDIX
Rapid Mood Screener (RMS)

- Can be completed by patients in less than 2 minutes, in or out of clinician’s office

<table>
<thead>
<tr>
<th>Item</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?</td>
<td>Yes</td>
</tr>
<tr>
<td>2. Did you have problems with depression before the age of 18?</td>
<td>Yes</td>
</tr>
<tr>
<td>3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?</td>
<td>Yes</td>
</tr>
<tr>
<td>4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?</td>
<td>Yes</td>
</tr>
<tr>
<td>5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?</td>
<td>Yes</td>
</tr>
<tr>
<td>6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?</td>
<td>Yes</td>
</tr>
</tbody>
</table>

When 4 or more items were endorsed, the new 6-item RMS had better estimated sensitivity (0.88), specificity (0.80), and predictive validity (PPV=0.80; NPV=0.88) than the Mood Disorders Questionnaire (MDQ) while reducing the number of items by more than half.
### Bipolar Depression Rating Scale (BDRS)

Clinician-administered assessment of **current** symptoms

<table>
<thead>
<tr>
<th>Severity of Disturbances to:</th>
<th>Mood</th>
<th>Motivation</th>
<th>Self-worth</th>
<th>Mood lability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sleep</td>
<td></td>
<td>Concentration/ memory</td>
<td>Suicidality</td>
<td>Motor drive</td>
</tr>
<tr>
<td>Appetite</td>
<td></td>
<td>Anxiety</td>
<td>Guilt</td>
<td>Increased speech</td>
</tr>
<tr>
<td>Social engagement</td>
<td></td>
<td>Anhedonia</td>
<td>Psychosis</td>
<td>Agitation</td>
</tr>
<tr>
<td>Energy/activity</td>
<td></td>
<td>Affect</td>
<td>Irritability</td>
<td></td>
</tr>
</tbody>
</table>
Hypomania Interview Guide (HIG)

Fifteen (15) questions addressing the following:

1. Elevated or expansive mood  (e.g., work-related, financial, or sexual)
2. Irritable mood
3. Increased self-esteem
4. Increased energy
5. Decreased need for sleep
6. Psychomotor agitation
7. Goal-directed work and activities
8. Social activities
9. Impulsive behavior and excessive pleasure-seeking
10. Sexual thoughts and activities
11. Rapid speech
12. Flights of ideas
13. Distractibility and concentration
14. Sharpened and unusually clear thinking
15. Decreased eating

Patient self-report assessing current (hypo)manic symptoms

<table>
<thead>
<tr>
<th>Points</th>
<th>Since you have been experiencing your current manic episode, have you almost every day had times when:</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>You felt sad, empty, tearful, down, or depressed?</td>
</tr>
<tr>
<td>2a</td>
<td>You were less interested in most activities?</td>
</tr>
<tr>
<td>2b</td>
<td>You had less pleasure doing the activities you used to enjoy?</td>
</tr>
<tr>
<td>3</td>
<td>You were slowed down in your speech, thoughts, or movements?</td>
</tr>
<tr>
<td>4a</td>
<td>You had fatigue?</td>
</tr>
<tr>
<td>4b</td>
<td>You felt without energy?</td>
</tr>
<tr>
<td>5a</td>
<td>You had feelings of worthlessness?</td>
</tr>
<tr>
<td>5b</td>
<td>You felt excessively guilty?</td>
</tr>
<tr>
<td>6</td>
<td>You wished you were dead, considered hurting yourself, made plans to commit suicide or attempted suicide?</td>
</tr>
</tbody>
</table>

**TOTAL =**

IF THE TOTAL NUMBER OF POINTS IS EQUAL TO OR GREATER THAN 3, THE PATIENT PRESENTS A PROBABLE (HYPO-)MANIC EPISODE WITH MIXED FEATURES

### Clinically Useful Depression Outcome Scale With **DSM-5** Mixed Features (CUDOS-M)

**Patient self-report assessing current (hypo)manic symptoms**

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Frequency of each symptom during the prior week</th>
</tr>
</thead>
<tbody>
<tr>
<td>I felt so happy and cheerful, it was like a high</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I had many brilliant, creative ideas</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I felt extremely self-confident</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I slept only a few hours but woke full of energy</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>My energy seemed endless</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I was much more talkative than usual</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I spoke faster than usual</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>My thoughts were racing through my mind</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I took on many new projects because I felt I could do everything</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I was much more social and outgoing than usual</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I did wild, impulsive things</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I spent money more freely than usual</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
<tr>
<td>I had many more thoughts and fantasies about sex</td>
<td><img src="table_frequencies.png" alt="Frequency Scale" /></td>
</tr>
</tbody>
</table>

### Hypomania Checklist (HCL-32)

Patient self-report that screens for **lifetime** (hypo)manic symptoms

<table>
<thead>
<tr>
<th>HCL-32</th>
</tr>
</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>
</tbody>
</table>

<table>
<thead>
<tr>
<th>HCL-32 (continued)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I am more flirtatious and/or am more sexually active</td>
</tr>
<tr>
<td>I talk more</td>
</tr>
<tr>
<td>I think faster</td>
</tr>
<tr>
<td>I make more jokes or puns when I am talking</td>
</tr>
<tr>
<td>I am more easily distracted</td>
</tr>
<tr>
<td>I engage in lots of new things</td>
</tr>
<tr>
<td>My thoughts jump from topic to topic</td>
</tr>
<tr>
<td>I do things more quickly and/or more easily</td>
</tr>
<tr>
<td>I am more impatient and/or get irritable more easily</td>
</tr>
<tr>
<td>I can be exhausting or irritating for others</td>
</tr>
<tr>
<td>I get into more quarrels</td>
</tr>
<tr>
<td>My mood is higher, more optimistic</td>
</tr>
<tr>
<td>I drink more coffee</td>
</tr>
<tr>
<td>I smoke more cigarettes</td>
</tr>
<tr>
<td>I drink more alcohol</td>
</tr>
<tr>
<td>I take more drugs (sedatives, anti-anxiety pills, stimulants)</td>
</tr>
</tbody>
</table>

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Mood Disorders Questionnaire (MDQ)

- 13 yes/no self-report questions (4 potential additional questions based on patient response)

- Screens for lifetime history of manic/hypomanic symptoms

- Shorter and possibly more accurate than the HCL-32

- However, the HCL may be better for detecting subthreshold hypomania symptoms

Altman Mania Rating Scale

Question 1
0  I do not feel happier or more cheerful than usual.
1  I occasionally feel happier or more cheerful than usual.
2  I often feel happier or more cheerful than usual.
3  I feel happier or more cheerful than usual most of the time.
4  I feel happier or more cheerful than usual all of the time.

Question 2
0  I do not feel more self-confident than usual.
1  I occasionally feel more self-confident than usual.
2  I often feel more self-confident than usual.
3  I feel more self-confident than usual.
4  I feel extremely self-confident all of the time.

Question 3
0  I do not need less sleep than usual.
1  I occasionally need less sleep than usual.
2  I often need less sleep than usual.
3  I frequently need less sleep than usual.
4  I can go all day and night without any sleep and still not feel tired.

Question 4
0  I do not talk more than usual.
1  I occasionally talk more than usual.
2  I often talk more than usual.
3  I frequently talk more than usual.
4  I talk constantly and cannot be interrupted.

Question 5
0  I have not been more active (either socially, sexually, at work, home or school) than usual.
1  I have occasionally been more active than usual.
2  I have often been more active than usual.
3  I have frequently been more active than usual.
4  I am constantly active or on the go all the time.