MORE THAN MEETS THE EYE: DIAGNOSING AND TREATING BIPOLAR DEPRESSION
Learning Objectives

• Optimize the differential diagnosis between unipolar and bipolar depression

• Employ evidence-based treatment strategies for patients with bipolar depression
The Mood Disorder Spectrum

<table>
<thead>
<tr>
<th>Depression</th>
<th>Depression with subsyndromal mania</th>
<th>Mixed states</th>
<th>Mania with subsyndromal depression</th>
<th>Mania</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Increasing #/severity of manic symptoms</td>
<td></td>
<td>Increasing #/severity of depressive symptoms</td>
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</tbody>
</table>

- 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 BP
- Individuals with unipolar depression and "a little bit of mania" are more likely to have an eventual diagnostic conversion to bipolar disorder.

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

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 twice as high for BD compared to MDD

Conus P et al. Bipolar Disord 2014;16(5):548-56;
Risk of Suicide Attempt Depends On Mood Phase

The graph illustrates the incidence of suicide attempts relative to euthymia across different mood phases:

- **Euthymic**: Lowest incidence
- **Subthreshold depression**: Slightly higher than euthymic
- **Major depressive episode**: Moderately higher
- **Mixed episode**: Highest incidence

These findings suggest that the risk of suicide attempt is highest during mixed episodes and lowest during euthymic states.
Diagnosis of Bipolar Depression
Is it bipolar or unipolar depression?
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

Excessive crying
More talkative
Elevated mood
Inflated self-esteem
Decreased need for sleep
Increased energy
Racing thoughts
Impulsivity
Risky behavior
Psychomotor agitation
Distractibility
Irritability
Suicidality
Depressed mood
Loss of interest in previously enjoyable activities
Weight loss or gain
Insomnia
Excessive sleepiness
Difficulty concentrating
Loss of energy
Excessive crying

Unipolar Depression

Bipolar Spectrum Disorders
So you think it’s unipolar depression?

• As many as 60% of patients with BPII 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 rediagnosed 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%

Progression to Bipolar Disorder From MDD With Subthreshold Hypomania

N=550 individuals followed for >1 year (mean follow-up: 17.5 years) after a diagnosis of major depression at intake.

19.6% of patients converted to bipolar disorder during follow-up

Symptoms Most Commonly Seen in Depression With Mixed Features (DMX)

Frequency among patients with DMX

- Excluded from DSM-5

Mixed Features: The exception or the rule?

Mixed features commonly encountered in adults with both major depressive disorder and bipolar disorder: The International Mood Disorders Collaborative Project

<table>
<thead>
<tr>
<th>Disorder</th>
<th>% of Individuals Who Met Criteria For Mixed Features During an Index Major Depressive Episode</th>
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<tbody>
<tr>
<td>MDD</td>
<td>26.0% (n=149)</td>
</tr>
<tr>
<td>BPII</td>
<td>34.0% (n=65)</td>
</tr>
<tr>
<td>BPI</td>
<td>33.8% (n=49)</td>
</tr>
</tbody>
</table>
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
More Common In Bipolar Depression

- Irritability
- Feelings of guilt
- History of suicide attempts
- History of previous depressive episodes
- Family history of Bipolar Disorder (BP)
- Early age of onset (<25 years)
- Early morning insomnia
- Shorter depressive episodes
- Psychomotor retardation (BP-I)
- Psychomotor agitation (BP-II)
- Comorbid personality disorder
- Overeating/weight gain
- Catatonic features
- Comorbid substance use disorder
- Hypersomnia
- Restlessness
- Melancholic features
- More previous depressive episodes
- MDD family history
- More Common In Bipolar Depression

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 can not 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.


### 32-Item Hypomania Checklist (HCL-32)

<table>
<thead>
<tr>
<th>Item</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>I need less sleep</td>
<td>I am more flirtatious and/or am more sexually active</td>
</tr>
<tr>
<td>I feel more energetic and more active</td>
<td>I talk more</td>
</tr>
<tr>
<td>I am more self-confident</td>
<td>I think faster</td>
</tr>
<tr>
<td>I enjoy my work more</td>
<td>I make more jokes or puns when I am talking</td>
</tr>
<tr>
<td>I am more sociable (make more phone calls, go out more)</td>
<td>I am more easily distracted</td>
</tr>
<tr>
<td>I want to travel and/or do travel more</td>
<td>I engage in lots of new things</td>
</tr>
<tr>
<td>I tend to drive faster or take more risks when driving</td>
<td>My thoughts jump from topic to topic</td>
</tr>
<tr>
<td>I spend more money/too much money</td>
<td>I do things more quickly and/or more easily</td>
</tr>
<tr>
<td>I take more risks in my daily life (in my work and/or other activities)</td>
<td>I am more impatient and/or get irritable more easily</td>
</tr>
<tr>
<td>I am physically more active (sport, etc.)</td>
<td>I can be exhausting or irritating for others</td>
</tr>
<tr>
<td>I plan more activities or projects</td>
<td>I get into more quarrels</td>
</tr>
<tr>
<td>I have more ideas, I am more creative</td>
<td>My mood is higher, more optimistic</td>
</tr>
<tr>
<td>I am less shy or inhibited</td>
<td>I drink more coffee</td>
</tr>
<tr>
<td>I wear more colorful and more extravagant clothes/make-up</td>
<td>I smoke more cigarettes</td>
</tr>
<tr>
<td>I want to meet or actually do meet more people</td>
<td>I drink more alcohol</td>
</tr>
<tr>
<td>I am more interested in sex, and/or have increased sexual desire</td>
<td>I take more drugs (sedatives, anti-anxiety pills, stimulants)</td>
</tr>
</tbody>
</table>
### 15-Item Hypomania Checklist (HCL-15)

<table>
<thead>
<tr>
<th>symptom</th>
</tr>
</thead>
<tbody>
<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, euphoric</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>

Mood Disorders Questionnaire (MDQ)

• 13 yes/no self-report answers

• 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

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

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 Depression: Efficacy
Mood Stabilizers

- No mood stabilizer is approved for use in depression of any kind (unipolar, mixed, bipolar)
- There are some data for the efficacy of lamotrigine or valproate for bipolar depression
- Lithium is well known for its anti-suicide effects; however, neither lithium nor carbamazepine monotherapy is recommended for the treatment of bipolar depression
Lithium

- Most effective drug for the treatment of recurrent depression and bipolar disorders
- Most stabilizing agent available
  - Little risk to worsen depression (like antipsychotics)
  - Little risk to worsen mania (like antidepressants)
- Anti-suicidal
  - Depression with mixed features is associated with high risk of suicidality
  - Lithium has been shown to prevent suicide, regardless of diagnosis
- May have side effects less dangerous than those associated with antipsychotics or other anticonvulsants
- Can be used in populations where mixed states are more prevalent
  - Pediatric (age 12+)
  - Postpartum
- Protective effect against neurodegenerative changes
- Randomized, controlled studies are lacking but observational studies support the use of lithium in mixed depression
- More clinical studies are needed

Sani G, Fiorillo A. CNS Spectr 2019; Epub ahead of print..
### Atypical Antipsychotics

<table>
<thead>
<tr>
<th></th>
<th>Evidence of efficacy in DMX</th>
<th>FDA-approved for BP depression</th>
<th>FDA-approved for BP mania</th>
<th>FDA-approved for BP maintenance</th>
<th>FDA-approved for MDD</th>
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<tbody>
<tr>
<td>Aripiprazole</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>Asenapine</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Brexpiprazole</td>
<td></td>
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<td></td>
<td>✓</td>
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<tr>
<td>Cariprazine</td>
<td>✓</td>
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<td>✓</td>
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<tr>
<td>Lurasidone</td>
<td>✓</td>
<td>✓</td>
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<td></td>
<td>✓</td>
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<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓</td>
<td>✓ (with fluoxetine)</td>
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<tr>
<td>Quetiapine</td>
<td>✓</td>
<td>✓</td>
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<tr>
<td>Risperidone</td>
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<td>✓</td>
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<tr>
<td>Ziprasidone</td>
<td>✓</td>
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<td></td>
<td></td>
<td>✓</td>
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</tbody>
</table>

**References:**
# Quetiapine in Bipolar Depression

<table>
<thead>
<tr>
<th>Study</th>
<th>MADRS WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al. 2005</td>
<td>-6.47 (-8.67; -4.27)</td>
</tr>
<tr>
<td>Thase et al. 2006</td>
<td>-4.07 (-6.03; -2.11)</td>
</tr>
<tr>
<td>Young et al. 2010</td>
<td>-4.29 (-6.28; -2.3)</td>
</tr>
<tr>
<td>McElroy et al. 2010</td>
<td>-3.71 (-6.22; -1.2)</td>
</tr>
<tr>
<td><strong>Quetiapine 600 pooled</strong></td>
<td><strong>-4.64 (-5.82; -3.46)</strong></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study</th>
<th>MADRS WMD (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calabrese et al. 2005</td>
<td>-6.13 (-8.33; -3.93)</td>
</tr>
<tr>
<td>Thase et al. 2006</td>
<td>-5.01 (-6.95; -3.07)</td>
</tr>
<tr>
<td>Young et al. 2010</td>
<td>-3.55 (-5.55; -1.55)</td>
</tr>
<tr>
<td>McElroy et al. 2010</td>
<td>-3.59 (-6.1; -1.08)</td>
</tr>
<tr>
<td>Suppes et al. 2010</td>
<td>-5.51 (-7.88; -3.14)</td>
</tr>
<tr>
<td><strong>Quetiapine 200 pooled</strong></td>
<td><strong>-4.76 (-5.75; -3.76)</strong></td>
</tr>
</tbody>
</table>

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

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Olanzapine-Fluoxetine Combination (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

Lurasidone in Bipolar Depression: Adjunct

Change From Baseline in MADRS (MMRM)

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

Placebo + Li/VPA (N=161)  ▲ Lurasidone + Li/VPA (N=179)
Baseline mean = 30.8  Baseline mean = 30.6
Mean daily dose of lurasidone: 66.3 mg (90% of participants received ≥60 mg)

Cariprazine for Bipolar Depression

What's the role of antidepressants?
Recommendations From the International Society for Bipolar Disorders (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

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 nonobese patients

Cardiovascular Disease and Hypertension Among Adults With Bipolar I Disorder

## BD Treatments: Side Effects

<table>
<thead>
<tr>
<th></th>
<th>LMG</th>
<th>LI</th>
<th>CBZ</th>
<th>VAL</th>
<th>Other</th>
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<tr>
<td><strong>BD Treatments</strong></td>
<td></td>
<td></td>
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<tr>
<td><strong>Stahl SM. Stahl's essential psychopharmacology: the prescriber's guide. 5th ed. 2018.</strong></td>
<td></td>
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<td>BD Treatments: Side Effects (cont.)</td>
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<td><strong>ZIP</strong></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
  - Arpiprazole
  - Clozapine
  - Gluphine
  - Risperidone
  - Ziprasidone

- Quetiapine
  - Olanzapine
  - Risperidone
  - Ziprasidone

Metabolic Changes With Lurasidone

Safety Population

Metabolic Changes With Lurasidone

**Glucose**

<table>
<thead>
<tr>
<th>Group</th>
<th>Median Change from Baseline (mg/dL)</th>
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<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>0.0</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg (n=140)</td>
<td>-1.0</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=143)</td>
<td>0.0</td>
</tr>
</tbody>
</table>

BL Mean 94.5 mg/dL  Placebo (n=148)

## Tolerability Profile of Cariprazine

<table>
<thead>
<tr>
<th>Adverse Event&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Bipolar Depression&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Bipolar Mania</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Placebo (n=323)</td>
<td>Cariprazine 1.5 mg (n=324)</td>
</tr>
<tr>
<td>Akathisia</td>
<td>8 (2.5)</td>
<td>19 (5.9)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>Restlessness</td>
<td>11 (3.4)</td>
<td>6 (1.9)</td>
</tr>
<tr>
<td>Extrapyramidal disorder</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Nausea</td>
<td>6 (1.9)</td>
<td>19 (5.9)</td>
</tr>
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</table>

<sup>a</sup>Based on the two fixed-dose studies with similar slow titration protocol (MD-53, -54); <sup>b</sup>occurring in ≥5% of patients in the cariprazine treatment groups and twice the incidence of placebo; <sup>c</sup>dose range of 3–12 mg/d.

Summar

• Unipolar and bipolar depression present with symptoms that are similar

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

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

• There are several treatment options for bipolar depression available with varying tolerability profiles