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

We Can Do Better: 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
Overview

• Review tactics to enhance timely and accurate diagnosis of bipolar disorder

• Discuss obesity as facilitating a "depression-prone" bipolar phenotype

• Discuss treatment avenues capable of mitigating depressive symptoms in bipolar disorder
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)
Pretest Question 1

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
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
Bipolar Spectrum Disorders: Prevalence in the National Comorbidity Survey Replication

<table>
<thead>
<tr>
<th>Disorder</th>
<th>12-Month Prevalence (%)</th>
<th>Lifetime Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD with mania</td>
<td>0.30</td>
<td>0.70</td>
</tr>
<tr>
<td>MDD with hypomania</td>
<td>0.80</td>
<td>1.60</td>
</tr>
<tr>
<td>MDD with subthreshold hypomania</td>
<td>2.20</td>
<td>6.70</td>
</tr>
<tr>
<td>MDD only</td>
<td>5.40</td>
<td>10.20</td>
</tr>
</tbody>
</table>

N = 9282 adults assessed in a national household survey of the US population conducted between February 2001 and April 2003.

MDD = major depressive disorder.

Diagnosing Bipolar Disorder Can Be Challenging

Initial diagnosis can take ≥10 years\(^1\)

Patients with bipolar disorder are more likely to present with symptoms of depression\(^2,3\)

Symptom overlap can lead to misdiagnosis, as depression symptoms are difficult to distinguish from MDD\(^4\)

One-third of patients are misdiagnosed with MDD\(^5\)

Comorbidities (eg, anxiety disorder, alcohol and substance abuse, cognitive or attention disorders, eating disorders) are common and complicate diagnosis\(^6\)

Longer Duration of Untreated Illness Is Associated With Higher Suicidality

Suicide attempts

Suicide attempters (%)

Duration of untreated illness

≤2 years  (n=65)  >2 years  (n=255)

Mean number of suicide attempts

Mean number of suicide attempts

≤2 years  (n=65)  >2 years  (n=255)

*p<0.05 vs. duration of untreated illness ≤2 years
Naturalistic study in patients with bipolar disorder (5-year follow-up)

Altamura et al. 2010.
Symptom Status in Bipolar Disorder: Weeks in Affective States During Follow-up

N = 146 patients with bipolar I disorder followed for 12.8 years and 86 patients with bipolar II disorder followed for 13.4 years.

# Differential Diagnosis of Bipolar and Unipolar Depression: A Probabilistic Approach

<table>
<thead>
<tr>
<th>Symptoms and signs</th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Consider more likely if ≥5 are present</strong></td>
<td><strong>Consider more likely if ≥4 are present</strong></td>
<td></td>
</tr>
<tr>
<td>Hypersomnia, increased daytime napping</td>
<td>Initial insomnia, reduced sleep</td>
<td></td>
</tr>
<tr>
<td>Hyperphagia, increased weight</td>
<td>Appetite loss and/or weight loss</td>
<td></td>
</tr>
<tr>
<td>Atypical symptoms (leaden paralysis)</td>
<td>Normal or increased activity levels</td>
<td></td>
</tr>
<tr>
<td>Psychotic features, guilt</td>
<td>Somatic complaints</td>
<td></td>
</tr>
<tr>
<td>Lability of mood/manic symptoms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rapid onset of depressive symptoms</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Course</th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;25 years</td>
<td>&lt;25 years</td>
<td></td>
</tr>
<tr>
<td>≥5 prior major depressive episodes</td>
<td>Long duration of episode (&gt;6 mo)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history</th>
<th>Bipolar Depression</th>
<th>Unipolar Depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive for bipolar disorder</td>
<td>Negative for bipolar disorder</td>
<td></td>
</tr>
</tbody>
</table>
Diagnosis of Bipolar Disorder: Changes in DSM-5

- Requires increased activity and energy as well as mood changes during manic and hypomanic episodes
- Includes new specifiers
  - "with mixed features"
  - "with anxious distress"
- Allows identification of full manic or hypomanic episode when symptoms emerge during antidepressant treatment
  - Symptoms must persist beyond the physiological effects of antidepressant

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Kraepelin conceptualised not only mood cycling up and down, but also thought processes and volition.

6 types of mixed state were identified:

- **Depressive or anxious mania** (depressed mood but elevated will and thought)
- **Excited depression** (depressed mood and will but elevated thought)
- **Manic with thought poverty** (elevated mood and will but decreased thought)
- **Manic stupor** (elevated mood but decreased will and thought)
- **Depression with flight of ideas** (depressed mood and thought but elevated will)
- **Inhibited mania** (elevated mood and thought but decreased will)

Studies That Opened Up Our Thinking

- Stanley Network Studies
- Munich Study
- NIMH Depression Collaborative Study
- STEP–BD Study
- BRIDGE Study
Specific DSM-IV Manic Symptoms During an Index Episode of Bipolar Depression in STEP-BD

Specific DSM-IV Manic Symptoms During an Index Episode of Bipolar Depression in STEP-BD

3-Fold Higher Rate of Bipolar Disorder in Individuals With MDD When Using Bipolar Specifier

Demographic Features of the Study Sample

<table>
<thead>
<tr>
<th>Country</th>
<th>Patients, No.</th>
<th>Hospitalized, %</th>
<th>Age, Mean (SD), Y</th>
<th>Male Sex, %</th>
<th>Bipolar DSM-IV-TR</th>
<th>Bipolar Specifier</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bosnia</td>
<td>200</td>
<td>46.5</td>
<td>46.3 (10.9)</td>
<td>32.5</td>
<td>45 (22.5)</td>
<td>111 (55.5)</td>
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<tr>
<td>Bulgaria</td>
<td>300</td>
<td>46.0</td>
<td>49.8</td>
<td>36.5</td>
<td>56 (18.7)</td>
<td>171 (57.0)</td>
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<tr>
<td>China</td>
<td>727</td>
<td>45.9</td>
<td>39.7 (14.4)</td>
<td>39.1</td>
<td>105 (14.4)</td>
<td>290 (39.9)</td>
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<tr>
<td>Egypt</td>
<td>306</td>
<td>24.2</td>
<td>37.7 (12.8)</td>
<td>49.0</td>
<td>42 (13.7)</td>
<td>144 (47.1)</td>
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<tr>
<td>Georgia</td>
<td>254</td>
<td>18.5</td>
<td>46.5 (15.0)</td>
<td>32.9</td>
<td>39 (15.4)</td>
<td>103 (40.6)</td>
</tr>
<tr>
<td>Germany</td>
<td>251</td>
<td>59.4</td>
<td>48.0 (12.3)</td>
<td>36.8</td>
<td>29 (11.6)</td>
<td>102 (40.6)</td>
</tr>
<tr>
<td>Iran</td>
<td>313</td>
<td>37.4</td>
<td>38.4 (12.3)</td>
<td>33.9</td>
<td>57 (18.2)</td>
<td>169 (54.0)</td>
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<tr>
<td>Korea</td>
<td>212</td>
<td>25.5</td>
<td>45.0 (14.5)</td>
<td>27.8</td>
<td>15 (7.1)</td>
<td>55 (25.9)</td>
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<tr>
<td>Macedonia</td>
<td>224</td>
<td>26.8</td>
<td>47.5 (13.3)</td>
<td>28.6</td>
<td>29 (12.9)</td>
<td>107 (47.8)</td>
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<tr>
<td>Morocco</td>
<td>317</td>
<td>20.8</td>
<td>39.7 (11.5)</td>
<td>38.3</td>
<td>55 (17.4)</td>
<td>148 (46.7)</td>
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<tr>
<td>The Netherlands</td>
<td>220</td>
<td>12.7</td>
<td>46.1 (13.7)</td>
<td>40.0</td>
<td>28 (12.7)</td>
<td>81 (36.8)</td>
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<tr>
<td>Pakistan</td>
<td>265</td>
<td>37.0</td>
<td>38.2 (12.0)</td>
<td>50.4</td>
<td>60 (22.6)</td>
<td>158 (59.6)</td>
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<tr>
<td>Portugal</td>
<td>311</td>
<td>11.9</td>
<td>45.9 (13.0)</td>
<td>25.7</td>
<td>45 (14.5)</td>
<td>172 (55.3)</td>
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<tr>
<td>Slovakia</td>
<td>297</td>
<td>57.6</td>
<td>48.4 (13.2)</td>
<td>38.0</td>
<td>50 (16.8)</td>
<td>166 (55.9)</td>
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<tr>
<td>Spain</td>
<td>655</td>
<td>25.5</td>
<td>47.2 (13.9)</td>
<td>33.1</td>
<td>100 (15.3)</td>
<td>324 (49.5)</td>
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<tr>
<td>Taiwan</td>
<td>420</td>
<td>14.8</td>
<td>45.3 (12.7)</td>
<td>27.2</td>
<td>64 (15.2)</td>
<td>149 (35.5)</td>
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<tr>
<td>Ukraine</td>
<td>297</td>
<td>73.7</td>
<td>46.9 (13.1)</td>
<td>29.6</td>
<td>65 (21.9)</td>
<td>156 (52.5)</td>
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<tr>
<td>Vietnam</td>
<td>66</td>
<td>37.9</td>
<td>40.7 (11.1)</td>
<td>51.5</td>
<td>19 (28.8)</td>
<td>41 (62.1)</td>
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<tr>
<td><strong>Total</strong></td>
<td><strong>5635</strong></td>
<td><strong>34.4</strong></td>
<td><strong>44.1 (13.7)</strong></td>
<td><strong>35.5</strong></td>
<td><strong>903 (16.0)</strong></td>
<td><strong>2647 (47.0)</strong></td>
</tr>
</tbody>
</table>

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
  – Individuals with subthreshold hypomania have a more severe illness course

• High impulsivity increases the rate of conversion to bipolar disorder

• BPII vs. MDD: distinct disorders or continuity on the mood spectrum?

Progression to Bipolar Disorder From MDD With Subthreshold Hypomania

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

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

• Approximately 20-55% of cases of MDD are characterized by lifetime symptoms of some degree of subthreshold hypomania

• Relative to those with "pure" depression, those with lifetime subthreshold hypomanic symptoms may have a more complex illness and a less favorable course and outcome
DSM-5 Criteria for MDE Remains the Same as DSM-IV-TR Criteria

Depressive criteria

• ≥5 of the following symptoms present during the same 2-week period and represent a change from previous functioning; ≥1 of the symptoms is either depressed mood or loss of interest or pleasure
  – Depressed mood most of the day
  – Markedly diminished interest or pleasure in activities
  – Significant weight loss when not dieting or weight gain or increase or decrease in appetite
  – Insomnia or hypersomnia
  – Fatigue or loss of energy
  – Feelings of worthlessness or excessive or inappropriate guilt
  – Diminished ability to think or concentrate or indecisiveness

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Changes in New DSM-5 Criteria: MDE With Mixed Features Specifier

Full criteria for an MDE and ≥3 of the following manic symptoms

- Elevated, expansive mood
- Inflated self-esteem or grandiosity
- More talkative than usual or pressure to keep talking
- Flight of ideas or racing thoughts
- Increase in energy or goal-directed activity (socially, sexually, or at work or school)
- Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, foolish business investments)
- Decreased need for sleep

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Not Included in Mixed Specifier

Symptoms that could overlap on either pole

• Distractibility
• Irritability
• Agitation
• Insomnia or hypersomnia
• Indecisiveness
Conceptualization of Pure and Mixed States in DSM-IV-TR and DSM-5

### DSM-IV-TR

**Manic**
- Elevated mood: ≥3, <5

**Mixed**
- Elevated mood + depressed mood: ≥3, ≥5

**Depressive**
- Depressed mood: <3, ≥5

### DSM-5

**Manic**
- Elevated mood + energy: ≥3, <5

**Manic with mixed features**
- Elevated mood + energy: ≥3

**Depressive with mixed features**
- Depressed mood or loss of interest: ≥3, ≥5

**Depressive**
- Depressed mood or loss of interest: <3, ≥5

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APA. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Text rev. 1994; APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
DSM-5: "With Anxious Distress" Specifier

- At least 2 symptoms during the majority of days of MDE
  - Feeling keyed up or tense
  - Feeling unusually restless
  - Difficulty concentrating because of worry
  - Fear that something awful may happen
  - Feeling that one might lose control of oneself

- Severity
  - Mild: 2 symptoms
  - Moderate: 3 symptoms
  - Moderate-severe: 4-5 symptoms
  - Severe: 4-5 symptoms + motor agitation

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Simplifying and Expediting the Diagnostic Process: Still a Long Way to Go?

DSM-5: Inter-Rater Reliability of Diagnoses From the Initial Field Trials (Adult Diagnoses)

Kappa

-0.1  0.0  0.1  0.2  0.3  0.4  0.5  0.6  0.7  0.8

Major neurocognitive disorder
Posttraumatic stress disorder
Complex somatic symptom disorder revised
Hoardung disorder
Bipolar I disorder
Binge eating disorder
Borderline personality disorder
Schizoaffective disorder
Mild neurocognitive disorder
Schizophrenia
Attenuated psychotic symptoms syndrome
Mild neurocognitive disorder
Alcohol use disorder
Bipolar II disorder
Mild traumatic brain injury
Obsessive compulsive personality disorder
Major depressive disorder
Antisocial personality disorder
Generalized anxiety disorder
Mixed anxiety-depressive disorder

Very good agreement
Good agreement
Questionable agreement
Unacceptable agreement

Diagnostic Differences Between Bipolar I and II

- **Hypomanic Episode (Bipolar II Disorder)**
  - Abnormally and persistently elevated mood, activity, and energy for 4 days
  - Clear change in functioning from usual non-depressed mood
  - Changes must be observable by others without marked impairment in social or occupational functioning

- **Manic Episode (Bipolar I Disorder)**
  - Abnormally and persistently elevated mood, activity, and energy for at least 1 week (less if there is hospitalization)
  - Must cause marked impairment in social or occupational functioning, require hospitalization, or include psychotic features

Identifying Bipolar Depression: Screening and Diagnostic Considerations

• Evaluate all patients with major depression for manic, hypomanic, and subthreshold symptoms
  – Ask about mood changes immediately before or after prior depressive episodes
  – Ask about prior periods of enhanced function
  – Ask about temporal relationship with antidepressants

• Consider screening tools
  – Mood Disorder Questionnaire (MDQ)
  – Bipolar Depression Rating Scale (BDRS)

• Obtain collateral history from a significant other
  – Relationship challenges between patient and significant other can complicate obtaining collateral information

Berk M et al. Bipolar Disord 2007;9:571-9;
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, reduced energy, reduced concentration, etc.
  – Mixed
    • Psychotic symptoms, lability, increased speech, etc.


<table>
<thead>
<tr>
<th>32-Item Hypomania Checklist (HCL-32)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I need less sleep</td>
</tr>
<tr>
<td>I feel more energetic and 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 or 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 more physically active (sports, etc.)</td>
</tr>
<tr>
<td>I plan more activities or projects</td>
</tr>
<tr>
<td>I have more ideas or 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 and/or makeup</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>
### 15-Item Hypomania Checklist (HCL-15)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less sleep</td>
<td></td>
</tr>
<tr>
<td>More drive or energy</td>
<td></td>
</tr>
<tr>
<td>More self-confidence</td>
<td></td>
</tr>
<tr>
<td>Increased social activity and work motivation</td>
<td></td>
</tr>
<tr>
<td>Increased physical activity</td>
<td></td>
</tr>
<tr>
<td>More plans and ideas</td>
<td></td>
</tr>
<tr>
<td>Less shy, less inhibited</td>
<td></td>
</tr>
<tr>
<td>More talkative than usual</td>
<td></td>
</tr>
<tr>
<td>More puns and jokes, faster thinking, more laughing</td>
<td></td>
</tr>
<tr>
<td>More irritable, impatient</td>
<td></td>
</tr>
<tr>
<td>Increased consumption of coffee, cigarettes</td>
<td></td>
</tr>
<tr>
<td>Increased consumption of alcohol</td>
<td></td>
</tr>
<tr>
<td>Extremely happy mood, euphoric</td>
<td></td>
</tr>
<tr>
<td>Increased sex drive, interest in sex</td>
<td></td>
</tr>
<tr>
<td>Overly active (eg, shopping, business, telephone calls, travelling, visiting people)</td>
<td>A depressed patient who endorses less than 7 items has a 93% likelihood of having MDD rather than BPII</td>
</tr>
</tbody>
</table>

He et al. Gen Hosp Psychiatry 2013; Epub ahead of print.
Bipolar Disorder and Comorbidities: The Rule Rather Than the Exception!

Bipolar Disorder and Metabolic Syndrome: Shared Etiology

Common Risk Factors and Mechanisms Identified in Mood Disorders and Metabolic Syndrome

- Insufficient access to primary and preventive health care
- Iatrogenic factors
- Habitual inactivity
- Neurometabolism (insulin resistance)
- Neuroinflammation (eg, proinflammatory cytokines)
- Oxidative stress
- Environmental hazards (eg, early childhood adversity)

- Obesity
- Hypertension
- Dyslipidemia
- Hyperglycemia

Phenotype

**Obesity + MDD**
- Atypical features
- More severe (e.g., suicide risk)
- Poor cognitive performance

**Obesity + BD**
- Predominance of depressive symptoms
- More severe (e.g., suicide risk)
- Anxiety symptoms
- Poor cognitive performance
Increased Rates of Metabolic Syndrome in Bipolar Disorder: An International Observation

NHANES III – Prevalence of NCEP III-defined metabolic syndrome in general population: 23.7%

Estimate of metabolic syndrome in bipolar disorder population: 20-66%

NHANES III = Third National Health and Nutrition Examination Survey.
NCEP III = National Cholesterol Education Program Adult Treatment Protocol.

Overweight/Obese Individuals With Bipolar Disorder Have Abnormal Brain Connectivity

Subject Groups

Healthy Controls
n = 26

First-Episode Mania
n = 28

*P<0.05, †P<0.01 between groups.

Excess Weight in Bipolar Disorder Is Associated With Proinflammatory Signature

Kynurenine and neopterin levels and the kynurenine/tryptophan ratio in patients with bipolar disorder or healthy controls

*P<0.025; †P<0.01 vs. patients with bipolar disorder who were of normal weight.

Investigation of the tryptophan-kynurenine metabolism pathway as a proxy of dysregulated inflammatory homeostasis in euthymic, overweight individuals with bipolar disorder (n = 78) compared with healthy controls (n = 156).

Obesity: A Brain Hazard

Minocycline

Anti-inflammatory cytokines
Antioxidants
Neurotrophic factors

Serotonin

Tryptophan

Kynurenine

Kynurenine acid

KAT

In astrocytes

IDO, Indoleamine-pyrrole 2,3-dioxygenase
KAT, kynurenine aminotransferase
KMO, kynurenine 3-monooxygenase
NMDAR, N-methyl-D-aspartate receptor
ROS, reactive oxygen species

IDO

Pro-inflammatory cytokines

Quinolinic acid

In microglia

Minocycline

Excitotoxicity

NMDAR

3-OH-kynurenine

3-OH-anthranilic acid

Antioxidants

Neuroprotection

Neurotoxicity

Soczynska, McIntyre et al. 2013.
Increased body mass index makes an impact on brain white-matter integrity in adults with remitted first-episode mania

C. N. Kuswanto, M. Y. Sum, G. L. Yang, W. L. Nowinski, R. S. McIntyre and K. Sim

BMI was negatively correlated with attention and psychomotor processing speed, as measured by the Digit Symbol Substitution Test ($p<0.01$)

Overweight/obese patients with bipolar disorder had significantly lower scores on the Verbal Fluency Test than patients of normal weight with bipolar disorder ($p<0.05$)

BMI = body mass index.

## FDA and EMA-Approved Agents for Bipolar Disorder

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>EMA</th>
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</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Divalproex (+ ER)</td>
<td>✓</td>
<td>✓a</td>
</tr>
<tr>
<td>Olanzapine*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Risperidone*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Quetiapine (+ XR)*</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Aripiprazole*</td>
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<td>Carbamazepine ERC</td>
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<td>Asenapine*</td>
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<table>
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<th>Drug</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>OFC</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Quetiapine (+ XR)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lurasidone*</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

### Acute depression

<table>
<thead>
<tr>
<th>Drug</th>
<th>FDA</th>
<th>EMA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>✓</td>
<td>✓b</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓c</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>✓</td>
<td>✓c</td>
</tr>
<tr>
<td>Quetiapine (+ XR)</td>
<td>✓</td>
<td>✓c  (adjunct) (mono)</td>
</tr>
<tr>
<td>Risperidone LAI*</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Ziprasidone (adjunct)</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Carbamazepine ERC</td>
<td>X</td>
<td>✓</td>
</tr>
<tr>
<td>Divalproex ER</td>
<td>X</td>
<td>✓d</td>
</tr>
</tbody>
</table>

### Maintenance

Note: licensed indications vary according to market; refer to local Prescribing Information

*Adjunctive (FDA only) and monotherapy

*aTreatment of manic episodes when lithium is not tolerated or contraindicated

*bFor prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes

*cFor prevention of manic episodes in patients who have responded to acute treatment

*dCould be considered in patients who have responded to the medicinal product for acute mania

EMA, European Medicines Agency; ERC, extended-release capsules; FDA, Food and Drug Administration; LAI, long-acting injectable; OFC, olanzapine-fluoxetine combination; XR, extended release

The Needs of Patients With Bipolar Disorder: Aspects of Care Patients Would Most Like to See Improved

Understanding Patients’ Needs, Interactions, Treatment, and Expectations (UNITE) global survey of 1300 patients with bipolar disorder.

Baseline Manic Symptom Severity in Depression Prior to Antidepressant Treatment

TEM, treatment-emergent mania; ADR, antidepressant responder; ADNR, antidepressant nonresponder.

Higher Risk for Treatment-Emergent Affective Switching

- Bipolar I > bipolar II
- History of antidepressant-induced mania
- Mixed depression
- Low TSH with TCA use
- Hyperthymic temperament
- TCA or SNRI use
- Absence of antimanic mood stabilizer
- Genetic factors
- Comorbid alcoholism
- Female gender + comorbid anxiety disorder

SNRI, serotonin-norepinephrine reuptake inhibitor; TCA, tricyclic antidepressant; TSH, thyroid-stimulating hormone.

Antidepressant Use in Bipolar Disorder

3 of the ISBD Task Force Recommendations

• 65 experts in bipolar disorder
  – 80-95% ranked each recommendation as "Essential/Important"

1. Antidepressant monotherapy for acute bipolar depression
   a. Avoid in bipolar I disorder
   b. Avoid in bipolar II disorder in the presence of ≥2 core manic symptoms

2. Adjunctive antidepressants for acute bipolar depression
   a. Permissible if history of positive antidepressant response
   b. Avoid in the presence of ≥2 core manic symptoms, psychomotor agitation, or rapid cycling

3. Adjunctive antidepressants for bipolar maintenance
   a. Permissible if patient relapses into depressive episode after stopping antidepressant therapy

Bipolar I Depression: MADRS Total Score Over 8 Weeks for Olanzapine, OFC, or Placebo

Week

Placebo (n=355)  
Olanzapine (n=351)  
OFC (n=82)  

Mean Change in MADRS Total Score

-20  -15  -10  -5  0

0  1  2  3  4  5  6  7  8

*P < .001. †P < .01 vs. placebo. ‡P < .05 OFC vs. olanzapine. OFC = olanzapine-fluoxetine combination.

Quetiapine in Bipolar Depression

*P < .05. **P < .01. ***P < .001 vs. placebo. Intent to treat analysis.

Lurasidone Monotherapy for Bipolar Depression

- 6-week trial of lurasidone or placebo
- Bipolar I depressed patients, with or without rapid cycling

Change in MADRS From Baseline

20-60 mg (n=166)* 80-120 mg (n=160)† Placebo (n=170)

 monuments: -15.4 -15.4 -10.7

mean modal dose 34.9mg/day. †Mean modal dose = 92.3 mg/day.

Add-on Lurasidone for Bipolar Depression

6-week trial of lurasidone (20-120 mg/day) or placebo added to lithium or divalproex in bipolar I depression

MMRM: $P < .01$.
MMRM = mixed-effect model repeated measure

Lurasidone Efficacious in Bipolar Depression With Subsyndromal Hypomania

**P < .01.

Differential Efficacy of Antimanic Agents in Individuals With DSM-5 Mixed Specifier?

B) ≥3 depressive features

<table>
<thead>
<tr>
<th></th>
<th>Asenapine</th>
<th>Placebo</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS rating ≥1, PANSS ≥2</td>
<td>*</td>
<td>56</td>
<td>66</td>
</tr>
<tr>
<td>MADRS rating ≥2, PANSS ≥3</td>
<td>**</td>
<td>40</td>
<td>12</td>
</tr>
<tr>
<td>MADRS rating ≥3, PANSS ≥4</td>
<td>*</td>
<td>66</td>
<td>16</td>
</tr>
</tbody>
</table>

n= 113 69 132

* *p≤0.05, **p≤0.01 vs. placebo

Bipolar I Depression: MADRS Total Score Over 8 Weeks for Aripiprazole or Placebo

Aripiprazole is not FDA-approved for acute bipolar depression. 

\( P = \text{NS at week 8; } *P \leq 0.05. \uparrow P < 0.01; \text{ vs. placebo.} \)

Ziprasidone Monotherapy Not Efficacious in Acute Bipolar Depression

Mean Change in MADRS

Study 1

Study 2

Weeks

Weeks

Ziprasidone (120-160 mg/d)
Ziprasidone (40-160 mg/d)
Placebo
Ziprasidone (40-80 mg/d)
Placebo

Ziprasidone is not FDA-approved for acute bipolar depression.

*P < .05.

Conventional Antipsychotics Increase Severity of Depression/Dysphoria

Antipsychotics: Adverse Events

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>ARI</th>
<th>ASE</th>
<th>CLZ</th>
<th>ILE</th>
<th>LUR</th>
<th>OLZ</th>
<th>QTP</th>
<th>RIS</th>
<th>ZIP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Metabolic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight gain</td>
<td>+/0</td>
<td>+/0</td>
<td>++++</td>
<td>++</td>
<td>+/0</td>
<td>+++</td>
<td>++</td>
<td>++</td>
<td>+/0</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Glucose dysregulation</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>+</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence/sedation</td>
<td>+</td>
<td>0/+</td>
<td>++++</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td>EPS</td>
<td>+</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0/+</td>
<td>+</td>
<td>0</td>
<td>++</td>
<td>+</td>
</tr>
<tr>
<td><strong>Hormonal</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prolactin</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>+/0</td>
<td>0</td>
<td>++</td>
<td>0</td>
</tr>
</tbody>
</table>

ASE = asenapine; CLZ = clozapine; ILE = iloperidone; OLZ = olanzapine; QTP = quetiapine; RIS = risperidone; EPS = extrapyramidal symptoms.
Metabolic Changes With Lurasidone

Cholesterol

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Mean</th>
<th>Median Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=147)</td>
<td>197.4 mg/dL</td>
<td>-3.0</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg (n=140)</td>
<td>196.0 mg/dL</td>
<td>0.0</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=144)</td>
<td>202.2 mg/dL</td>
<td>-3.0</td>
</tr>
</tbody>
</table>

Triglycerides

<table>
<thead>
<tr>
<th>Group</th>
<th>Baseline Mean</th>
<th>Median Change From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=147)</td>
<td>125.2 mg/dL</td>
<td>-2.0</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg (n=140)</td>
<td>132.4 mg/dL</td>
<td>3.0</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg (n=144)</td>
<td>133.9 mg/dL</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Safety Population

Metabolic Changes With Lurasidone

**Glucose**

<table>
<thead>
<tr>
<th>Group</th>
<th>BL Mean</th>
<th>Median Change From Baseline (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo (n=148)</td>
<td>94.5 mg/dL</td>
<td>0.5</td>
</tr>
<tr>
<td>Lurasidone 20-60 mg</td>
<td>94.3 mg/dL</td>
<td>-1.0</td>
</tr>
<tr>
<td>Lurasidone 80-120 mg</td>
<td>94.7 mg/dL</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Safety Population

## NNT vs. NNH

<table>
<thead>
<tr>
<th>OFC vs. PBO</th>
<th>NNT = 4</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Effect</strong></td>
<td><strong>NNH</strong></td>
</tr>
<tr>
<td>Weight gain</td>
<td>7</td>
</tr>
<tr>
<td>Increased appetite</td>
<td>13</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>10</td>
</tr>
<tr>
<td>Asthenia</td>
<td>10</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>8.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>QUE vs. PBO</th>
<th>NNT = 5</th>
<th>NNT = 6</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Effect</strong></td>
<td><strong>NNH (600 mg/day)</strong></td>
<td><strong>NNH (300 mg/day)</strong></td>
</tr>
<tr>
<td>Dry mouth</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Sedation</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Somnolence</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7</td>
<td>11</td>
</tr>
<tr>
<td>Constipation</td>
<td>14</td>
<td>13</td>
</tr>
</tbody>
</table>

## NNT vs. NNH (continued)

<table>
<thead>
<tr>
<th>LUR vs. PBO</th>
<th>NNT = 5</th>
<th>NNH (20-60 mg/day)</th>
<th>NNH (80-120 mg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse Effect</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>18</td>
<td>12</td>
<td></td>
</tr>
<tr>
<td>Extrapyramidal symptoms</td>
<td>40</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Sedation</td>
<td>80</td>
<td>19</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>39</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>154</td>
<td>24</td>
<td></td>
</tr>
<tr>
<td><strong>Adj LUR vs. Adj PBO</strong></td>
<td>NNT = 7</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Adverse Effect</strong></td>
<td>NNH</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Akathisia</td>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somnolence</td>
<td>23</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Novel Treatments for Bipolar Depression

- Modafinil/armodafinil
- Pramipexole
- N-acetylcysteine
- Ketamine
- Riluzole
- Insulin sensitizers
- Anti-inflammatory agents

Adjunctive Levothyroxine in Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Study

*\( p<0.05 \) vs. placebo (ITT; LOCF)

Adjunctive levothyroxine (300 µg/day) or placebo in patients with bipolar I or II disorder
HAM-D, Hamilton rating scale for depression

Stamm et al. 2013.
## Treatment of Acute Bipolar Depression

### LEVEL 1A: Established efficacy*
- Quetiapine monotherapy (bipolar disorder I & II)
- Lurasidone monotherapy (bipolar disorder I)
- Lurasidone or quetiapine adjunctive to lithium or divalproex (bipolar disorder I)

### LEVEL 1B: Established efficacy, but with safety concerns*
- Olanzapine-fluoxetine (bipolar disorder I)

*Note. Tolerability limitations include sedation and weight gain.

### LEVEL 2: Established tolerability, but limited efficacy*
Consult specialist
- Lithium (bipolar disorder I)
- Lamotrigine adjunctive to lithium (bipolar disorder I)
- Lamotrigine (bipolar disorder I)
- 2-drug combination of above medications

*Note. Efficacy limitations include negative randomized controlled trails but positive meta-analyses.
LEVEL 3: If levels 1 and 2 are ineffective or if treatment is not tolerated*
- Electroconvulsive therapy (ECT)

*Note. Consideration merited due to clinical need, despite even greater efficacy/tolerability limitations than levels 1 and 2 treatments.

LEVEL 4: If levels 1-3 are ineffective or if treatment is not tolerated
- Transcranial magnetic stimulation (TMS)
- Antimanic therapy + (FDA-approved medication for major depression)*
- Pramipexole
- Adjunctive: modafinil, thyroid, or stimulants
- 3-drug combination

*Note. There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression.
Adjunctive Armodafinil in Bipolar Depression

- 8-week randomized comparison of armodafinil 150 mg/day (n=128) vs. placebo (n=129) added to lithium, olanzapine, or divalproex for bipolar depression

- 2 negative studies

*P= .027 (ANCOVA) vs. placebo. †P= .044 (ANOVA) and P= .074 (ANCOVA) vs. placebo.

Armodafinil is not FDA-approved for the treatment of bipolar depression.

ANCOVA = analysis of covariance; ANOVA = analysis of variance; IDS-C$_{30}$ = 30-Item Inventory of Depressive Symptomatology, Clinician-Rated.

Pramipexole in Bipolar Depression: Adjunct

### Effect of lisdexamfetamine on metabolic parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Baseline Mean (SD)</th>
<th>Week 4 Mean (SD)</th>
<th>Main effect of time p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>28.5 (5.8)</td>
<td>27.9 (5.7)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>84.0 (19.6)</td>
<td>82.3 (19.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4.6 (0.4)</td>
<td>4.7 (0.6)</td>
<td>0.739</td>
</tr>
<tr>
<td>Insulin (pmol/L)</td>
<td>39.9 (31.2)</td>
<td>35.0 (28.4)</td>
<td>0.250</td>
</tr>
<tr>
<td>Total cholesterol (mmol/L)</td>
<td>4.9 (1.0)</td>
<td>4.7 (0.9)</td>
<td>0.011</td>
</tr>
<tr>
<td>LDL (mmol/L)</td>
<td>3.0 (0.7)</td>
<td>2.9 (0.7)</td>
<td>0.044</td>
</tr>
<tr>
<td>HDL (mmol/L)</td>
<td>1.4 (0.3)</td>
<td>1.3 (0.3)</td>
<td>0.015</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.1 (0.6)</td>
<td>1.1 (0.4)</td>
<td>0.382</td>
</tr>
<tr>
<td>Ghrelin (pg/mL)</td>
<td>35.8 (13.7)</td>
<td>39.6 (23.7)</td>
<td>0.485</td>
</tr>
<tr>
<td>Adiponectin (pg/mL)</td>
<td>1.3 x 10⁷ (6.9 x 10⁶)</td>
<td>1.3 x 10⁷ (7.2 x 10⁶)</td>
<td>0.708</td>
</tr>
<tr>
<td>Resistin (pg/mL)</td>
<td>15292.7 (4620.2)</td>
<td>17339.9 (6345.9)</td>
<td>0.124</td>
</tr>
<tr>
<td>Leptin (ng/mL)</td>
<td>7.6 (6.9)</td>
<td>5.5 (5.2)</td>
<td>0.047</td>
</tr>
</tbody>
</table>

4-week, flexible dose, open-label study (n=40) in adults with stable bipolar disorder and comorbid ADHD. HDL, high-density lipoprotein; LDL, low-density lipoprotein.

McIntyre et al. 2013.
Adjunctive Lisdexamfetamine Benefits ADHD Symptom Severity and Metabolic Parameters in Stable Bipolar Disorder

ADHD-RS (mean) total score

Baseline | Week 1 | Week 2 | Week 3 | Week 4

Lisdexamfetamine (n=40)

†p<0.001 vs. baseline
4-week, flexible dose, open-label study in adults with stable bipolar disorder and comorbid ADHD. ADHD-RS, attention deficit hyperactivity disorder-self report scale.

McIntyre et al. 2013.
Empirically Tested Psychotherapies for Bipolar Disorder

- Cognitive behavioral therapy (CBT)
- Psychoeducation (group)
- Psychoeducation (individual)
- Family-focused therapy (FFT)
- Interpersonal and social rhythm therapy (IPSRT)

Adapted from Geddes et al. Lancet 2013;381:1672-82.
High Rate of Treatment Switch in Bipolar I Disorder: EMBLEM Study

Time to First Treatment Switch

Non-switchers (%)

<table>
<thead>
<tr>
<th>Days</th>
<th>0</th>
<th>30</th>
<th>60</th>
<th>90</th>
<th>120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-switchers</td>
<td>46%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Week 12

N = 3459 patients.
Antipsychotics, anticonvulsants, and/or lithium.
EMBLEM = European Mania in Bipolar Longitudinal Evaluation of Medication.

Changes in functional impairment scores before and after intervention in patients with bipolar disorder

Higher scores indicate greater impairment. Functional remediation program consisting of 21 weekly sessions lasting 90 minutes. Change for the functional remediation group was significantly different from change for the treatment-as-usual group (Pillai's Trace=.065; F=6.51, P=.002).

SE = standard error.

Summary

• Mixed features are common

• Mixed features and cardiometabolic syndrome increase mixed features?

• Avoid antidepressants in BD MDE mixed