Fixing the Mix-Up Over Mixed Depression

Diagnosing and Treating DSM-5 Defined Mixed Features in Mood Disorders
Learning Objectives

• Utilize evidence-based strategies to identify patients with mixed depression

• Optimize treatment strategies for patients with mixed depression
Overview

• Rationale for supplanting mixed states with mixed specifier: déjà-vu all over again!
• Clinical implications of mixed features in mood disorders
• Treating mixed features in mood disorders
Pre-Poll Question 1

I feel competent **diagnosing** patients with mixed 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 mixed depression.

1. 1 (strongly disagree)
2. 2
3. 3
4. 4
5. 5 (strongly agree)
Pretest Question 1

In the recently released *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5), "mixed states" is replaced with "mixed specifier." Rationales for this revision include:

1. The real world presentation of mixed states was not captured in the DSM-IV
2. Rates of misdiagnosis of bipolar disorder were very high based on DSM-IV criteria
3. Mixed states were being inappropriately treated
4. 1 and 2 only
5. 2 and 3 only
6. All of the above
Kate is a 26-year-old patient with bipolar depression who is currently showing some manic symptoms. According to the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, the most common subsyndromal manic symptom is:

1. Decreased need for sleep
2. Flight of ideas/racing thoughts
3. Distractibility
4. Increased activity
5. High-risk activity
Considerations for the Mood Spectrum

- Subthreshold hypomania during MDE in MDD
- Capture subthreshold episode types
- Spectrum

BD NOS
- Increased energy/activity
- Duration, symptom count
- Allow mixed hypomania

Bipolar II
- Increased energy/activity
- Unipolar mania

MDD
- Subthreshold features in MDD
- Specifier "with mixed features"
- Cyclothymia and other subthreshold presentations
- Developmental issues

MDE, major depressive episode;
MDD, major depressive disorder;
BD NOS, bipolar disorder not otherwise specified.
Kraepelin Conceptualized Affective States as a Continuum

Kraepelin conceptualized not only mood cycling up and down, but also thought processes and volition.

6 types of mixed states 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)

**Pure mania** (flight of ideas, euphoria, hyperactivity)

**Pure depression** (thought inhibition, depressive mood, weakness of volition)

### Conceptualization of Pure and Mixed States in DSM-IV-TR and DSM-5

#### DSM-IV-TR

<table>
<thead>
<tr>
<th>Core symptoms</th>
<th>Elevated mood</th>
<th>Elevated mood + depressed mood or loss of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic</td>
<td>≥3</td>
<td>≥3, &gt;5</td>
</tr>
<tr>
<td>Depressive</td>
<td>&lt;5</td>
<td>&lt;3, &gt;5</td>
</tr>
</tbody>
</table>

**DSM-IV-TR**

- **Manic**
- **Mixed**
- **Depressive**

#### DSM-5

<table>
<thead>
<tr>
<th>Core symptoms</th>
<th>Elevated mood + energy</th>
<th>Elevated mood + energy</th>
<th>Elevated mood or loss of interest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manic</td>
<td>≥3</td>
<td>≥3</td>
<td>≥3, &gt;5</td>
</tr>
<tr>
<td>Depressive</td>
<td>&lt;5</td>
<td>&lt;3</td>
<td>&lt;3, &gt;5</td>
</tr>
</tbody>
</table>

**DSM-5**

- **Manic**
- **Manic with mixed features**
- **Depressive with mixed features**
- **Depressive**

---

Main Changes For "Bipolar and Related Disorders" in DSM-5 Compared to DSM-IV-TR

<table>
<thead>
<tr>
<th></th>
<th>DSM-IV-TR</th>
<th>DSM-5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Specific chapter</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Increased activity/energy</td>
<td>Not core mania criteria</td>
<td>Yes, core mania criteria</td>
</tr>
<tr>
<td>Mixed episodes</td>
<td>Mania subtype categorical</td>
<td>Modifier* (specifier?) for either depressive or manic episodes</td>
</tr>
<tr>
<td>Antidepressant switching</td>
<td>Not bipolar</td>
<td>Bipolar</td>
</tr>
<tr>
<td>Additional &quot;specifiers&quot;</td>
<td></td>
<td>Anxiety, suicide</td>
</tr>
<tr>
<td>Other bipolar disorders</td>
<td>NOS</td>
<td>Other unspecified bipolar and related disorders</td>
</tr>
</tbody>
</table>

Reasons for Supplanting "Mixed States" with "Mixed Specifier"

- Real world presentation of mixed states not aligned with DSM-IV-TR description
- Bipolar disorder: high rates of misdiagnosis
- Suicidality and mixed states
- Inappropriate treatment of mixed states (e.g., antidepressants)
Individuals With DSM-5 Defined Mixed Features: High Unemployment Rate

Unemployment rate for patients with pure mania vs. mania with MFS

MFS, DSM-5 defined mixed features.

McIntyre et al. International Mood Disorders Collaborative Project. 2014.
Individuals With DSM-5 Defined Mixed Features: More Cardiovascular Disease

Prevalence of cardiovascular disease in patients with pure mania vs. mania with MFS

MFS, DSM-5 defined mixed features.

McIntyre et al. International Mood Disorders Collaborative Project. 2014.
Evidence Base Supporting Dimensionality in Mood Disorders

- Stanley Network Studies
- Munich Study
- NIMH Depression Collaborative Study
- STEP-BD Study
- BRIDGE Study

NIMH, National Institute of Mental Health;  
STEP-BD, Systematic Treatment Enhancement Program for Bipolar Disorder;  
BRIDGE, Bipolar Disorders: Improving Diagnosis, Guidance and Education.
Subsyndromal, Minor Depressive, and Hypomanic Symptoms Predominate

146 Bipolar I Patients Followed for 12.8 years

86 Bipolar II Patients Followed for 13.4 years

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.

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 Among 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>
</tr>
<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>
</tr>
<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>
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<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>
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<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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<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>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>
</tr>
<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>
</tr>
<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>
</tr>
<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>
</tr>
<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>

Mixed features specifier (MFS) was operationalized as a score ≥1 on 3 or more select items on the Young Mania Rating Scale (YMRS) or ≥1 on 3 select items on the Montgomery-Åsberg Depression Rating Scale (MADRS) or the Hamilton Depression Rating Scale (HAMD-17) during an index major depressive episode (MDE) or a hypo/manic episode, respectively.

McIntyre RS et al. J Affective Disord 2015;172C:259-64.
MDD and Subthreshold Bipolarity

- 10-year prospective study; n=2,210 subjects (14–24 years at baseline)
- Subthreshold BD = MDD + hypo/manic symptoms, but never having met criteria for (hypo)mania
- Among 488 respondents with MDD, 60% had pure MDD and 40% had subthreshold BD
- Subthreshold BD cases had:
  - Significantly increased family history of mania
  - Higher rates of nicotine dependence, alcohol use disorder, and panic disorder
- Subthreshold BD converted more often to BD than to pure MDD

BD, bipolar disorder; MDD, major depressive disorder.

MDD → BD Continuum

- Approximately 20–55% of MDD cases are characterized by lifetime symptoms of some degree of subthreshold hypomania
- Compared to those with "pure" depression, those with lifetime subthreshold hypomanic symptoms may have more complex illness and less favorable course and outcome
Low Level of Agreement on the Diagnostic Phenotype of MDD: Mixed Features Point of Confusion

DSM-5: inter-rater reliability of diagnoses from the initial field trials (adult diagnoses)

- Major neurocognitive disorder
- Posttraumatic stress disorder
- Complex somatic symptom disorder revised
- Hoarding disorder
- Bipolar I disorder
- Binge eating disorder
- Borderline personality disorder
- Schizoaffective disorder
- Mild neurocognitive disorder
- Schizophrenia
- Attenuated psychotic symptoms syndrome
- 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

Kappa:
- Very good agreement
- Good agreement
- Questionable agreement
- Unacceptable agreement

Pooled data presented from DSM-5 field trials sites, except for the diagnosis of complex somatic symptoms disorder revised, hoarding disorder, binge eating disorder, schizoaffective disorder, attenuated psychotic symptoms syndrome, bipolar II disorder, obsessive–compulsive disorder, antisocial personality disorder, and generalized anxiety disorder.

Changes in New DSM-5 Criteria: MDE With Mixed Features Specifier

Full criteria for an MDE and ≥3 of these 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 (either socially, at work or school, or sexually)
• Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
• Decreased need for sleep

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Anxiety Distress Specifier Also Frequently Applies to BD and MDD

• With anxious distress:
  - Feeling keyed up or tense
  - Difficulty concentrating because of worry
  - Fear that individual might lose control of him- or herself
  - Mild: 2 symptoms
  - Moderate: 3 symptoms
  - Feeling unusually restless
  - Fear that something awful might happen
  - Moderate-severe: 4-5 symptoms
  - Severe: 4-5 symptoms + motor agitation

APA. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. 2013.
Commonly Used Terminology

**Diagnostic criteria**

**Mixed episode (DSM-IV)**
State in which the full criteria for both a manic and a depressive episode are met simultaneously

**Mixed features (DSM-5)**
A specifier that can be added to manic, hypomanic, or depressive episodes e.g., "manic episode with mixed (depressive) features"

**Describing patients**

**Mixed mania/mania with subsyndromal depression**
Presence of depressive symptoms during a manic episode

**Manic/hypomanic episode with depressive symptoms**

**Mixed depression/depressive episode with subsyndromal mania**
Presence of manic symptoms during a depressive episode

**MDE with hypomanic symptoms**

MDE, major depressive episode.

Symptoms that could overlap on either pole:

- Distractibility
- Irritability
- Insomnia or hypersomnia per se
- Indecisiveness
- Anxiety
## Probabilistic Approach to Bipolar Depression

**Bipolar I depression more likely if ≥5:**

<table>
<thead>
<tr>
<th>Symptomatology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia</td>
</tr>
<tr>
<td>Hyperphagia</td>
</tr>
<tr>
<td>Psychomotor retardation</td>
</tr>
<tr>
<td>Other &quot;atypical&quot; symptoms</td>
</tr>
<tr>
<td>Psychosis and/or pathological guilt (OR=3.3)</td>
</tr>
<tr>
<td>Mood lability or manic symptoms</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Onset and Course</th>
</tr>
</thead>
<tbody>
<tr>
<td>Earlier onset (&lt;25 years) (OR=1.9)</td>
</tr>
<tr>
<td>Multiple (≥5) depressive episodes</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family History</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bipolar disorder (OR=2.6)</td>
</tr>
</tbody>
</table>

Confirmation of specific numbers requires further study.
Subsyndromal Hypomanic Symptoms Increase Risk of Switching


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

Obesity Changes Phenotype of Mood Disorder

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

Rosenblat and McIntyre, 2015.
Antidepressant Use in Bipolar Disorder

ISBD Task Force Recommendations

1. 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

2. 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

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

See ISBD Task Force description at http://www.isbd.org/task-forces/past-task-forces.

Antidepressant Use in Bipolar Disorder: The ISBD Task Force Consensus Report.
Presented at International Conference on Bipolar Disorders. 2013.
Antidepressant Use in Bipolar Disorder (cont)

**ISBD Task Force Recommendations**

4. Antidepressant-Induced Switching to Mania/Hypomania or Mixed Features and Rapid Cycling
   a. Monitor patient and discontinue antidepressants in response to emergent mania, hypomania, or psychomotor agitation
   b. Discourage antidepressants if there is a history of antidepressant-emergent mania/hypomania or mixed episodes
   c. Avoid if there is high mood instability or a history of rapid cycling

5. Antidepressant Use in Mixed States
   a. Avoid during manic or depressive episodes with mixed features
   b. Avoid in patients with predominantly mixed states
   c. Discontinue if a mixed state emerges

6. Antidepressant Classes and Increased Risk of Mood Switching (SNRIs and TCAs)
   a. Permissible only after trials of other antidepressants tried and if patient is closely monitored for switch or mood destabilization

See ISBD Task Force description at http://www.isbd.org/task-forces/past-task-forces.

Mixed Features Specifier Common in Bipolar Depression

- 56.1% met the severity criterion (YMRS score ≥4) for mixed features
- (43.1%) met an alternative item-based criterion (YMRS score ≥2 on 2 or more items)
- Mixed features were more likely
  - Female
  - White
  - Earlier age at onset of bipolar illness
  - History of rapid cycling
  - Higher baseline levels of anxiety

YMRS, Young Mania Rating Scale.

Lurasidone Effective in Bipolar Depression With Hypomanic Symptoms (DSM-5 Specifier)

MADRS responder rates (6-week LOCF-endpoint): groups with and without subsyndromal hypomania

**p<0.01

Lurasidone for the Treatment of Major Depressive Disorder With Mixed Features: A Randomized, Double-Blind, Placebo-Controlled Study

Double-Blind Phase

Study dosing
Days 1–7: 20 mg/day
Days 8–43: flexible, 20–60 mg/day

Lurasidone 20–60 mg/day
Placebo

Screening
Baseline
Day 1

Planned N=200 (100/arm)

FPI: Sep 2011
LPO: Oct 2014

12 Weeks

Extension Study 306 (US Sites)

FPI, first patient in; LPO, last patient out; US, United States.
Key Inclusion Criteria

• All patients (aged 18–75 years) were required to meet criteria for major depressive disorder plus 2 or 3 of the following manic symptoms (occurring on most days over the last 2 weeks or longer):

  • Elevated, expansive mood
  • Inflated self-esteem or grandiosity
  • More talkative than usual or pressure to keep talking
  • Flight of ideas or subjective experience that thoughts are racing
  • Increase in energy or goal-directed activity (socially, at work or school, or sexually)
  • Increased or excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments)
  • Decreased need for sleep (feeling rested despite sleeping less than usual; in contrast to insomnia)
Lurasidone Highly Effective in MDD With Mixed Features

LS Mean Change From Baseline

Placebo (N=100)
Baseline
Week 1
Week 2
Week 3
Week 4
Week 5
Week 6

Lurasidone (N=108)

BL mean = 33.3
BL mean = 33.2

*P<0.05; **P<0.01; ***P<0.001.

ITT population.

MADRS scale range, 0-60.
Mean daily dose of lurasidone was 36.2 mg/day.

Lurasidone Reduces Hypomanic Severity in Adults With MDD and Mixed Features

Mean Change From Baseline

BL mean = 10.3

BL mean = 11.1

**P<0.01.

YMRS, Young Mania Rating Scale.

Lurasidone Reduces Anxiety Severity in Adults With MDD and Mixed Features

Mean Change From Baseline

Placebo (n=99)  Lurasidone (n=106)

BL mean = 16.7  BL mean = 17.0

-5.6  -9.9***

***P<0.001
HAM-A, Hamilton Anxiety Rating Scale.

HAM-A, Hamilton Anxiety Rating Scale.

Lurasidone Reduces Global Illness Severity in Adults With MDD and Mixed Features

Mean Change From Baseline

- Placebo (n=80)
  - BL mean = 20.5
  - Mean change = -6.4

- Lurasidone (n=80)
  - BL mean = 19.9
  - Mean change = -10.7***

***P<0.001.

SDS, Sheehan Disability Scale.

Olanzapine Monotherapy Is Efficacious in the Treatment of Bipolar Depression With Mixed Features

Remission rate by mixed features category. Abbreviation: NNT=number needed to treat. Mixed feature was defined by the number of baseline Young Mania Rating Scale items with scores ≥1. Remission was defined as the patient whose Montgomery–Åsberg Depression Rating Scale total score was ≤12 at 6 weeks. Treatment comparison p-values are from Fisher’s exact test. Interaction p-values are from the Breslow–Day test.

Bipolar I and II Depression: Quetiapine XR

***P<0.001 vs. placebo
XR, extended release.

Suppes T. J Affective Disord 2010;121:106.
Ziprasidone vs. placebo: 6-week change in MADRS from baseline. Error bars indicate standard deviation. Treatment response by categorical group was 52.9% for ziprasidone vs. 28.9% for placebo ($\chi^2 = 4.29$, df = 1, p = 0.04). Treatment remission by categorical group was 50.0% for ziprasidone vs. 18.4% for placebo ($\chi^2 = 8.05$, df = 1, p = 0.0045).

Asenapine in Mania With Depressive Symptoms (DSM-5 Specifier)

Cut-offs used to define depressive symptom severity in patients with ≥3 depressive features: mild (score ≥1 for MADRS items and ≥2 for PANSS item), moderate (score ≥2 MADRS, ≥3 PANSS) and severe (score ≥3 MADRS, ≥4 PANSS) symptoms; remission defined as MADRS ≤12; post hoc analysis.

### Adverse Effect Profiles for Atypical Antipsychotics

<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>QUE</th>
<th>RIS</th>
<th>ZIP</th>
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<tbody>
<tr>
<td><strong>METABOLIC</strong></td>
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</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>
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<td>++</td>
<td>0</td>
<td>0</td>
<td>+++</td>
<td>+</td>
<td>+</td>
<td>0</td>
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<td>Glucose dysregulation</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Somnolence/sedation</td>
<td>+</td>
<td>0/+</td>
<td>++++</td>
<td>+</td>
<td>0</td>
<td>+++</td>
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<td>EPS</td>
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<td>0/+</td>
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<td><strong>CARDIOVASCULAR</strong></td>
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<tr>
<td>Myocarditis/cardiomyopathy</td>
<td>0</td>
<td>0</td>
<td>+/0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>QTc prolongation</td>
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<td>0</td>
<td>+/0</td>
<td>+</td>
<td>0</td>
<td>+/0</td>
<td>+</td>
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<td>Prolactin</td>
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<td>+/0</td>
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</tbody>
</table>

Number of + symbols signifies extent of adverse event; 0 neutral


No Faster Recovery From Mixed Depression in Bipolar Disorder When Antidepressants Are Added to Mood Stabilizers (STEP-BD)

355 STEP-BD entrants with major depression + 1 or more manic symptoms

Kaplan-Meier Curve for Time to Recovering/Recovered by Antidepressant Use
(without 26 subjects who were on antidepressant at 2nd CMF)

N=145 w/AD
N=190 w/o AD

Logrank Test
Chi-square = 0.205
DF = 1
P-value = 0.651
Treatment-Resistant Bipolar Depression: Randomized Controlled Trial of Electroconvulsive Therapy vs. Algorithm-Based Pharmacological Treatment

A linear mixed-effects analysis showed that the mean score at 6 weeks was 6.6 points lower in the ECT group (SE=2.05, 95% CI=2.5–10.6, p=0.002).
### 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)

*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

*Efficacy limitations include negative randomized controlled trials but positive meta-analyses

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# Treatment of Acute Bipolar Depression

<table>
<thead>
<tr>
<th>LEVEL 3: If levels 1 and 2 are ineffective or treatment not tolerated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Electroconvulsive therapy (ECT)</td>
</tr>
<tr>
<td>*Consideration merited due to clinical need, despite even greater efficacy/tolerability limitations than level 1 and 2 treatments</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>LEVEL 4: If levels 1-3 are ineffective or if treatment is not tolerated</th>
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</thead>
<tbody>
<tr>
<td>- Transcranial magnetic stimulation (TMS)</td>
</tr>
<tr>
<td>- Antimanic therapy + (FDA-approved medication for major depression)*</td>
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<tr>
<td>- Pramipexole</td>
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<tr>
<td>- Adjunctive: modafinil, thyroid, or stimulants</td>
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<tr>
<td>- 3-drug combination</td>
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<tr>
<td>*There is inadequate information, including negative trials, to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinil, or omega-3 fatty acids for bipolar depression</td>
</tr>
</tbody>
</table>
Summary

• Mood disorders are multidimensional

• Zone of delimitation (i.e., division point) between bipolar disorder and MDD does not exist organically

• MDD has prominent hypomanic features

• Antidepressants are hazardous when treating MDE with hypomanic features

• Antipsychotics are preferred in treating MDE with hypomanic features