Update on Depression and Mixed Symptoms

Trisha Suppes, MD, Ph.D.
Stanford University School of Medicine
VA Palo Alto Health Care System
Palo Alto, California
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What Was Wrong With the DSM-IV Criteria for Mixed Episode?
Spectrum of Mixed States

Classic Manic Episode

Euthymia

DSM-IV Mixed Episode

MDE
History of Mixed States

• Jules Falret (1861): First to use term “mixed state”
• Mixed episodes were recognized by Weygandt and Kraepelin in 1899

• DSM-IV (1994): Requires coexistence of the full symptomatology of a manic and depressive episode

• Other descriptions include: depressive or anxious mania, excited depression, and agitated depression
Bipolar I disorder is a dimensional disease

Mania

Mania with depressive symptoms

Depression

Mania

Normal fluctuation

Depression

Bipolar disorder – symptoms

- Hopelessness
- High activity/energy level
- Loss of energy
- Anxiety
- Diminished need for sleep
- Worthlessness
- Diminished pleasure
- Elevated mood
- Disordered thoughts
- Irritability
- Suicidal thoughts
- Euphoria
- Extremely talkative
- Depressed mood
- Dysphoria
- Agitation
- Insomnia
- Impulsivity
Consequences of not recognizing Mixed Symptoms – problems w DSM-IV

• Underestimation of suicide risk

• Inappropriate treatment selection

• Failure to identify those with unipolar disorder at increased risk of progression to bipolar disorder
Patients with depressive symptoms in manic episodes have a higher suicide risk than those with pure manic episodes.

**Suicidal ideation and suicide attempts in bipolar disorder**

<table>
<thead>
<tr>
<th></th>
<th>Suicidal ideation</th>
<th>Suicide attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Non-mixed bipolar disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=84)</td>
<td>29.8</td>
<td></td>
</tr>
<tr>
<td><strong>Mixed bipolar disorder</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=60)</td>
<td>66.7</td>
<td>46.7</td>
</tr>
</tbody>
</table>

***p<0.001

A study of 144 patients with bipolar disorder followed for ≤20 years

How did we get to DSM 5

• Long history in European case series and reports of mixed symptoms not being confined to manic episodes

• We just needed the data to demonstrate this
Prevalence of Mixed Hypomania
n=14,328 visits in 908 Patients

<table>
<thead>
<tr>
<th>Series 1</th>
<th>Depressed</th>
<th>Hypomanic*</th>
<th>Mixed Hypomanic</th>
<th>Euthymic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IDS-C &gt;=15 YMRS &lt;12</td>
<td>YMRS &gt;=12</td>
<td>YMRS &gt;=12 IDS-C &gt;=15</td>
<td>IDS-C &lt;15 YMRS &lt;12</td>
</tr>
<tr>
<td></td>
<td>34</td>
<td>3.1</td>
<td>4.2</td>
<td>58</td>
</tr>
</tbody>
</table>

*Does not include Mixed Hypomania

“The cheerful and mournful or anxious mood are not simple opposites that are mutually exclusive, but they may mix with each other in the most different ways”

Emil Kraepelin, 1921
MDD/Mixed: A Conceptual Model

BPI, bipolar I disorder; BPII, bipolar II disorder; MDE, major depressive episode.
Prevalence of DSM-5 Mixed Features* During Major Depressive Episodes

International Mood Disorders Collaborative Project

Ziprasidone treatment in depressive mixed states in bipolar disorder type II or MDD

Change from baseline in MADRS score

* $p<0.05$ vs. placebo; ** $p<0.001$ vs. placebo


MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder
Lurasidone in MDD with mixed features:
Change in MADRS total score

Effect size = 0.80

Baseline mean = 33.3
Baseline mean = 33.2

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

LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; MDD, major depressive disorder

Do Antidepressants Worsen MDD-MF?

Retrospective history of antidepressant-induced mania/hypomania in BRIDGE-II-Mix Study

VA Palo Alto Bipolar and Depression Research Program; CCR; and CSP NODES Staff

Trisha Suppes, MD, PhD
Michael Ostacher, MD, MPH
Grace Fischer, BS
Elena Nikolaev
David Grimm, BA, BS
Jeff Nagy, MS, MHA
Victoria Cosgrove, PhD
Karishma Raju
Karen Bratcher, RN, MSN
Alda Vicencio, RN, BSN
Ami Patel, MPH
Perrin French, MD
DSM-5: Mixed Specifier With Depressive Features

• If full criteria are met for a manic episode or hypomaniac episode and at least 3 of the following symptoms are present during the majority of days of the current or most recent episode of mania or hypomania (last 1 week or 4 days):

DSM-5: Mixed Specifier With Depressive Features

- Prominent dysphoria or depressed mood
- Diminished interest or pleasure in all activities
- Psychomotor retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive/inappropriate guilt
- Suicidal ideation, attempt, or plan

Mixed Specifier
With Hypomanic Features

• If predominantly Depressed, full criteria are met for a Major Depressive Episode and at least 3 of the following symptoms are present nearly every day during the episode:

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Mixed Specifier

*With Hypomanic Features*

- Elevated, expansive mood
- Inflated self-esteem or grandiosity
- More talkative or pressured speech
- Flight of ideas or thoughts are racing
- Increase in energy or goal-directed activity
- Increased activities that have a high potential for painful consequences
- Decreased *need* for sleep
Not Included in Mixed Specifier

Symptoms that could overlap on either pole:

• Distractibility
• Irritability
• Insomnia or hypersomnia *per se*
• Indecisiveness
• Agitation
Lurasidone in MDD with mixed features: Efficacy with high levels of irritability

Lurasidone in MDD with mixed features: Efficacy with high levels of irritability

Irritability group:
- **Lurasidone** (n=22)
  - Baseline mean = 34.0
- **Placebo** (n=21)
  - Baseline mean = 34.2

**Non-irritability group**:
- **Lurasidone** (n=86)
  - Baseline mean = 33.0
- **Placebo** (n=79)
  - Baseline mean = 33.1

**Effect size**:
- Lurasidone: 1.41
- Placebo: 0.66

Irritability criteria: YMRS items 5 & 9 ≥2

LS, least squares; MADRS, Montgomery-Åsberg Depression Rating Scale; MDD, major depressive disorder

Lurasidone in MDD with mixed features: Nature of manic symptoms

- Flight of ideas
- Pressured speech
- Decreased need for sleep
- Increased energy
- Elevated mood
- Increased involvement in risky activities
- Inflated self esteem


MDD, major depressive disorder
## Mood States During 14,310 Visits

<table>
<thead>
<tr>
<th>Mood State</th>
<th>Number of Visits</th>
<th>Percentage of Total Visits</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pure Dep. (YMRS≤2; IDS-C≥15)</td>
<td>2774</td>
<td>19.4%</td>
</tr>
<tr>
<td>Mixed Dep. (2&lt;YMRS&lt;12; IDS-C≥15)</td>
<td>2139</td>
<td>14.9%</td>
</tr>
<tr>
<td>Hypomania/Mania (YMRS≥12)</td>
<td>1045</td>
<td>7.3%</td>
</tr>
<tr>
<td>Euthymia (YMRS&lt;12; IDS-C&lt;15)</td>
<td>8352</td>
<td>58.4%</td>
</tr>
</tbody>
</table>
Olanzapine in bipolar I depression with manic symptoms


Interaction $p=0.045$

Percentage of patients in remission

- Total
  - Placebo: 33.3% ($n=219$)
  - Olanzapine: 48.7% ($n=228$)
  - $p=0.001$

- Non-Mixed
  - Placebo: 35.9% ($n=153$)
  - Olanzapine: 45.6% ($n=169$)
  - $p=0.089$

- Mixed
  - Placebo: 27.3% ($n=66$)
  - Olanzapine: 57.6% ($n=59$)
  - $p<0.001$
Lurasidone treatment of bipolar depression with subsyndromal hypomania: Post hoc analysis

Change from baseline in MADRS score (MMRM; mITT)


LS, least squares; MADRS, Montgomery–Åsberg Depression Rating Scale; mITT, modified intention-to-treat; MMRM, mixed model for repeated measures
Lurasidone Treatment of Bipolar Depression with Mixed Features: Post hoc analysis

Lurasidone for Major Depressive Disorder with Mixed Features

Mean dose = 36.2 mg/day

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

Suppes T et al., *AJP* in Advance (doi: 10.1176/appi.ajp.2015.15060770)