Clinical Relevance of the
DSM-5 Mixed Features Specifier:
Diagnostic and Therapeutic Implications

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Disclosure

The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).

- The off-label use of antidepressants for the treatment of bipolar disorder; and aripiprazole, asenapine, cariprazine, and lamotrigine for the treatment of bipolar depression will be discussed.
- No drugs are currently FDA-approved for the treatment of major depressive disorder with mixed features; lurasidone, asenapine, quetiapine, quetiapine XR, aripiprazole, ziprasidone, lamotrigine, valproate, lithium, cariprazine, olanzapine, fluoxetine, bupropion, modafinil, armodafinil, pramipexole, omega-3 fatty acids, inositol, ketamine, N-acetylcysteine, ramelteon, celecoxib, topiramate, and risperidone will be discussed.

Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.

This activity has been independently reviewed for balance.
Kraepelin’s Continuum of Pure and Mixed Mood States

<table>
<thead>
<tr>
<th>Thinking</th>
<th>Mood</th>
<th>Behavior</th>
<th>Classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overactive</td>
<td>Elevated</td>
<td>Overactive</td>
<td>Pure Mania</td>
</tr>
<tr>
<td>Overactive</td>
<td>Depressed</td>
<td>Overactive</td>
<td>Depressive or Anxious Mania</td>
</tr>
<tr>
<td>Overactive</td>
<td>Depressed</td>
<td>Underactive</td>
<td>Excited Depression</td>
</tr>
<tr>
<td>Underactive</td>
<td>Elevated</td>
<td>Overactive</td>
<td>Manic with Thought Poverty</td>
</tr>
<tr>
<td>Underactive</td>
<td>Elevated</td>
<td>Underactive</td>
<td>Manic Stupor</td>
</tr>
<tr>
<td>Underactive</td>
<td>Depressed</td>
<td>Underactive</td>
<td>Depression with Flight of Ideas</td>
</tr>
<tr>
<td>Overactive</td>
<td>Elevated</td>
<td>Underactive</td>
<td>Inhibited Mania</td>
</tr>
<tr>
<td>Underactive</td>
<td>Depressed</td>
<td>Underactive</td>
<td>Pure Depression</td>
</tr>
</tbody>
</table>
**DSM-5 “Mixed Features” Specifier**

- Replaces *DSM-IV-TR* “mixed episodes”
- > 3 symptoms of opposite polarity that do not overlap with the syndromal pole
- Overlap symptoms can’t count twice:
  - Distractibility, indecision, insomnia, irritability

- Can occur in bipolar I (mania or depression) or bipolar II (hypomania or depression)
- Can occur in (unipolar) major depressive disorder
Assessing Mixed States

- Careful past history, use of corroborative historians when available
- Must systematically inquire about individual symptoms of depression and of mania/hypomania
  - S I G E C A P S and D I G F A S T
- No single measurement scale
  - MADRS or HAM-D or PHQ-9 for depression, YMRS for mania
- Differentiate adverse drug effects (eg, akathisia, insomnia, antidepressant withdrawal states) from affective symptoms
- Rule out diagnostic confounding factors (eg, active substance misuse, steroids, thyroid disease)
- Note presence or absence of dysfunction attributable to mania/hypomania symptoms (vs depressive symptoms)

MADRS = Montgomery-Åsberg Depression Rating Scale; HAM-D = Hamilton Rating Scale for Depression; PHQ-9 = Patient Health Questionnaire 9-item; YMRS = Young Mania Rating Scale.
Mixed States Worsen Prognosis

- Mixed hypomania + depression 2× as common as mania + depression; over one-half of patients with hypomania symptoms manifest mixed features
- Younger age at onset
- Recurrent across episodes
- Greater risk for suicidality
- More functional impairment, unemployment
- More alcohol/substance use comorbidity
- More cardiovascular disease
- Often follows a rapid cycling course

Prevalence of *DSM-5* Mixed Features* during Major Depressive Episodes

**International Mood Disorders Collaborative Project**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Prevalence (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDD (n=149)</td>
<td>26.0%</td>
</tr>
<tr>
<td>BD I (n=65)</td>
<td>34.0%</td>
</tr>
<tr>
<td>BD II (n=49)</td>
<td>33.8%</td>
</tr>
</tbody>
</table>

MDD = major depressive disorder; BD = bipolar disorder.

*DSM-5 Mixed features specifier defined via extracting YMRS, MADRS, or HAM-D items
Longer Time to Recovery in Mixed vs Pure Bipolar Depression

131 Korean BD I or II inpatients

Mean time to recovery = 5.1 months
Mean time to recovery = 7.0 months
Mean time to recovery = 7.7 months

Overall group comparison: $P=.0018$
Depressive mixed state vs pure depressed: $P=.022$
Subthreshold mixed vs pure depressed: $P=.035$

Progression to Bipolar Disorder from MDD with Subthreshold Hypomania


N=550 patients followed for a mean of 17.5 years after index major depressive episode.

19.6% of patients converted to bipolar disorder during follow-up.
Do Antidepressants Worsen MDD with Mixed Features?

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

<table>
<thead>
<tr>
<th>Mixed Features (+)</th>
<th>Mixed Features (-)</th>
</tr>
</thead>
<tbody>
<tr>
<td>53.8% (n=52)</td>
<td>26.7% (n=135)</td>
</tr>
</tbody>
</table>

OR = 3.21 (95% CI = 1.65–6.24)

P < .0001

BRIDGE = Bipolar Disorders: Improving Diagnosis, Guidance and Education.
Lurasidone for MDD with Mixed Features

Baseline mean MADRS: Placebo = 33.3, Lurasidone = 33.2.

### MDD with Mixed Features: Expert Guideline Recommendations


<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-Line</strong></td>
<td><strong>Monotherapy</strong>: lurasidone, asenapine, quetiapine, quetiapine XR, aripiprazole, ziprasidone</td>
</tr>
<tr>
<td><strong>Second-Line</strong></td>
<td><strong>Monotherapy</strong>: lamotrigine, valproate, lithium, cariprazine, olanzapine</td>
</tr>
<tr>
<td></td>
<td>Lithium, lamotrigine, or valproate + atypical antipsychotic</td>
</tr>
<tr>
<td></td>
<td>Lithium + valproate</td>
</tr>
<tr>
<td></td>
<td>Lithium or valproate + lamotrigine</td>
</tr>
<tr>
<td></td>
<td>Olanzapine + fluoxetine</td>
</tr>
</tbody>
</table>
### MDD with Mixed Features: 
**Expert Guideline Recommendations (cont’d)**

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Third-Line</strong></td>
<td><strong>Monotherapy:</strong> carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Lithium + carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Lithium + pramipexole</td>
</tr>
<tr>
<td></td>
<td>ECT</td>
</tr>
<tr>
<td></td>
<td>Lithium or lamotrigine or valproate or atypical antipsychotic + bupropion or SSRI or MAOI</td>
</tr>
<tr>
<td></td>
<td>Adjunctive modafinil, armodafinil, pramipexole</td>
</tr>
<tr>
<td></td>
<td>Adjunctive folic acid, inositol, ketamine, N-acetylcysteine, omega-3 fatty acids, ramelteon, or celecoxib</td>
</tr>
<tr>
<td><strong>Generally NOT recommended</strong></td>
<td><strong>Monotherapy:</strong> antidepressants or topiramate</td>
</tr>
<tr>
<td></td>
<td>Carbamazepine + olanzapine or risperidone</td>
</tr>
</tbody>
</table>

Most Syndromally Depressed Bipolar Patients Have Subthreshold Mixed Features

**DSM-IV** manic symptoms during an index episode of bipolar depression in **STEP-BD** (N=1380)

Poorer Outcomes with Antidepressants in Bipolar Depression with Subthreshold Mixed Features

355 STEP-BD entrants with major depression with ≥1 manic symptoms

Interaction Effect: Antidepressant use x # of mania symptoms at baseline = higher YMRS score after 3 months (P=.003)

Stanley Bipolar Network: Antidepressants exacerbate mania when low-grade baseline mania symptoms are present

F=4.5, df=2, 169, P<.01

Are Antidepressants Efficacious in Bipolar Depression? 2011 Meta-Analysis

<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant, n/N</th>
<th>Placebo, n/N</th>
<th>Relative Risk (fixed), 95% CI</th>
<th>Weight, %</th>
<th>Relative Risk (fixed), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nemeroff et al(^{42}) (2001)</td>
<td>29/69</td>
<td>15/43</td>
<td>18.01</td>
<td>1.20 (0.74–1.97)</td>
<td></td>
</tr>
<tr>
<td>Shelton and Stahl(^{41}) (2004)</td>
<td>5/20</td>
<td>1/10</td>
<td>1.30</td>
<td>2.50 (0.34–18.63)</td>
<td></td>
</tr>
<tr>
<td>Tohen et al(^{27}) (2003)</td>
<td>40/82</td>
<td>115/351</td>
<td>42.43</td>
<td>1.49 (1.14–1.95)</td>
<td></td>
</tr>
<tr>
<td>Sachs et al(^{39}) (2007)</td>
<td>32/163</td>
<td>40/169</td>
<td>38.26</td>
<td>0.83 (0.55–1.25)</td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>334</td>
<td>573</td>
<td>100.00</td>
<td>1.20 (0.98–1.47)</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 106 (antidepressant), 171 (placebo)
Test for heterogeneity: \( \chi^2_3 = 6.10 \ (P = .11) \), \( I^2 = 50.8\%
Test for overall effect: \( Z = 1.72 \ (P = .09) \)

NNT = number needed to treat.
Meta-Analysis: *Do Antidepressants Induce Mania?*

**Likelihood of Affective Polarity Switch**

<table>
<thead>
<tr>
<th>Study/Subcategory</th>
<th>Antidepressant, n/N</th>
<th>Placebo, n/N</th>
<th>Relative Risk (fixed), 95% CI</th>
<th>Weight, %</th>
<th>Relative Risk (fixed), 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cohn et al (1989)</td>
<td>2/60</td>
<td>1/29</td>
<td>3.97</td>
<td>3.97</td>
<td>0.97 (0.09–10.23)</td>
</tr>
<tr>
<td>Nemeroff et al (2001)</td>
<td>4/74</td>
<td>3/43</td>
<td>11.16</td>
<td>11.16</td>
<td>0.77 (0.18–3.30)</td>
</tr>
<tr>
<td>Shelton and Stahl (2004)</td>
<td>1/20</td>
<td>0/10</td>
<td>1.93</td>
<td>1.93</td>
<td>1.57 (0.07–35.46)</td>
</tr>
<tr>
<td>Amsterdam et al (2005)</td>
<td>2/17</td>
<td>1/8</td>
<td>4.00</td>
<td>4.00</td>
<td>0.94 (0.10–8.92)</td>
</tr>
<tr>
<td>Sachs et al (2007)</td>
<td>18/163</td>
<td>20/169</td>
<td>57.77</td>
<td>57.77</td>
<td>0.93 (0.51–1.70)</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>416</td>
<td>610</td>
<td>100.00</td>
<td>100.00</td>
<td>0.97 (0.62–1.53)</td>
</tr>
</tbody>
</table>

Total events: 32 (antidepressant), 44 (placebo)

Test for heterogeneity: $\chi^2_5 = 0.30 \ (P = 1.00), I^2 = 0$

Test for overall effect: $Z = 0.13 \ (P = .90)$

**NNH = 200**

NNH = number needed to harm.
Assessing Individual Patient Candidacy for Antidepressant Use in Bipolar Disorder

<table>
<thead>
<tr>
<th>Favors Antidepressant Use</th>
<th>Discourages Antidepressant Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>BD II</td>
<td>BD I</td>
</tr>
<tr>
<td>Pure depressed episodes</td>
<td>Mixed features</td>
</tr>
<tr>
<td>Absence of rapid cycling</td>
<td>Past year rapid cycling</td>
</tr>
<tr>
<td>Absence of recent mania/hypomania</td>
<td>Mania/hypomania in past 2–3 months</td>
</tr>
<tr>
<td>Absence of comorbid alcohol/substance use disorders</td>
<td>Alcohol or substance use comorbidity</td>
</tr>
<tr>
<td>Prior favorable antidepressant response</td>
<td>Suboptimal responses to prior antidepressants</td>
</tr>
<tr>
<td>No history of antidepressant-induced mania</td>
<td>History of antidepressant-induced mania/hypomania</td>
</tr>
</tbody>
</table>

Lurasidone for Bipolar Depression with Mixed Features

Change from Baseline in MADRS Score (MMRM):
Patients with and without Mixed Features at Baseline (mITT population)

*P<.05; **P<.01; ***P<.001.
LS = least-squares; mITT = modified intention-to-treat; MMRM = mixed model for repeated measures.
Depression During Mania

Treatment Response to Lithium or Divalproex

Alan C. Swann, MD; Charles L. Bowden, MD; David Morris, PhD; Joseph R. Calabrese, MD; Frederick Petty, MD, PhD; Joyce Small, MD; Steven C. Dilsaver, MD; John M. Davis, MD

**Background:** Little information exists from controlled studies about clinical characteristics that predict treatment response in mania. The presence of depressive symptoms during manic episodes may be associated with poor response to psychopharmacological treatments. This is an investigation of the relation between depressive symptoms and treatment response in acute manic episodes.

**Methods and Design:** In a parallel-group, double-blind study, 179 patients hospitalized for acute manic episodes were randomized to receive divalproex sodium, lithium carbonate, or placebo (ratio, 2:1:2). The study patients with and without depressive symptoms at baseline according to nurse- or physician-rated scales.

**Results:** Depressive symptoms were associated with poor antimanic response to lithium and with better response to divalproex. This was not due to differences in overall severity of illness, substance abuse, gender, age, or history.

**Conclusions:** These data suggest that even a modest level of pretreatment depression-related symptoms is a robust predictor of lithium nonresponse, and is associated...
Olanzapine vs Placebo in DSM-5 Mania with Mixed Features


Improvement from Baseline in Mania vs Depressive Symptoms at Week 3
Asenapine vs Placebo for Mania with DSM-5 Mixed Features: A Post Hoc Analysis

Change in Depressive Symptoms

Change in Mania Symptoms

*P < .05; **P < .01 vs placebo.
Quetiapine vs Placebo for Bipolar II Mixed Hypomania

Group x time interaction: $P = .015$

Group x time interaction: $P = .069$

Mean dose = 290 ± 108 mg/day

Bilateral ECT in Bipolar Mixed State Patients

- Open trial in 197 patients at the University of Pisa
- Unresponsive to at least 1 trial (> 16 weeks) of 2 mood stabilizers and/or antipsychotics and/or antidepressants

Response: 41.6%
Remission: 30.5%

Treatment Approach to Depressive Episodes with Mixed Features

• **Diagnostic/Clinical Considerations**
  – Highly recurrent episodes
  – Polarity-proneness
  – Family history of bipolar disorder
  – Heightened suicidality risk
  – Substance misuse

• **Independent Treatment of Common Comorbidities**
  – Substance use disorders, anxiety disorders, borderline personality disorder

• **Avoid Antidepressants in BD I or BD II MDE-MF; Consider Whether Antidepressants May Be Worsening MDD-MF**

• **Watch for Polarity Conversion in MDD-MF, Especially in First 5 Years**

• **Evidence-based Pharmacotherapies**
  – BD-MF: divalproex > lithium; most second-generation antipsychotics
  – Role of ECT
  – MDD-MF: lurasidone, ziprasidone, asenapine, quetiapine, olanzapine
Conclusions

• Modern rediscovery of Kraepelin’s notion that mixed features fall along a continuum from “pure” mania to “pure” depression
• *DSM-5* construct of “mixed features” applicable to BD I, BD II, and MDD patients
• Monitor risk for polarity conversion in MDD-MF
• Consider “probabilistic approach” to bipolar diagnosis alongside symptoms of mania/hypomania
• Beware the risk of antidepressants when depressive and (any) mania symptoms coexist
• Favor evidence-based treatments for mood episodes involving mixed features