Managing Bipolar Depression: An Evidence-Based Approach

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Main Changes for Bipolar and Related Disorders in *DSM-5* Compared to *DSM-IV-TR*

1. **Separate chapter** for Bipolar and Related Disorders

2. **Increased activity/energy** added as core mood elevation symptom (Criterion A)

3. The **“with mixed features” specifier** added for Manic, Hypomanic, and Major Depressive Episodes

4. **Manic Episode with mixed features** replaces Mixed Episode
Main Changes for Bipolar and Related Disorders in *DSM-5* Compared to *DSM-IV-TR*

5. **Antidepressant switching:** Full Manic/Hypomanic Episode emerging during antidepressant treatment and persisting beyond physiological treatment effect now sufficient for Manic/Hypomanic Episode

6. The “*with anxious distress*” specifier added for Manic, Hypomanic, and Major Depressive Episodes

7. The “*level of concern for suicide*” specifier added

8. **Other Specified Bipolar and Related Disorders** added, which along with Unspecified Bipolar and Related Disorder replaces Bipolar Disorder Not Otherwise Specified
Diagnostic Challenges in Bipolar Disorder

• Symptoms of bipolar depression overlap with unipolar depression; bipolar depressive presentations may be misdiagnosed as unipolar major depression

• Complexities of defining and diagnosing hypomania
  – Not experienced as “abnormal”
  – Difficult to diagnose retrospectively (especially without history from significant other)
Depressive Presentations at Increased Risk for Bipolar Outcome

- Acute onset, abrupt offset of depression
- Early onset of first depression (age 25 or younger)
- Family history of bipolar disorder
- Postpartum depression
- Seasonal affective disorder
- Antidepressant-induced hypomania or mania\textsuperscript{a}
- Recurrent MDD
- Atypical depression

\textsuperscript{a} Counts toward bipolar diagnosis if persists beyond expected physiological antidepressant duration (DSM-5, but not DSM-IV-TR). MDD, major depressive disorder.

What Is the Best Treatment for Bipolar Disorder?

- Treatment that results in the fewest, briefest, or mildest episodes and side effects and does not induce switch

- Primary therapeutic objectives:
  - Treat acute mania, depression, mixed episodes to remission
  - Prevent recurrences of illness
  - Restore function

- Combination treatment often required during acute and maintenance treatment
Pharmacotherapy of Bipolar Depression

- Mood stabilizers, including Li, VAL, and LTG (risk of inefficacy and/or side effects)
- Certain atypical antipsychotics (risk of more severe side effects)
- Antidepressants, including SSRIs, SNRIs, and MAOIs (risks of inefficacy, hypo/manic switch)
- Novel treatments (risk of inefficacy)

Li, lithium; LTG, Lamotrigine; MAOI, monoamine oxidase inhibitor; SNRI, serotonin norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; VAL, valproate.
Antidepressants in Bipolar I: Clinical Practice versus Guidelines

- 85% of physicians would use an antidepressant in patients with symptoms of depression and no other risk factors for bipolar I
- 55% were not concerned that their choice of treatment would lead to manic episode
- 5% thought no greater risk of treatment-emergent mood disorder when treating depression in patients with bipolar I versus MDD
- If patient had depression and risk factors for bipolar I, 54% would still prescribe an antidepressant as monotherapy

Antidepressants Most Common Initial Treatments for Bipolar Disorder Patients in United States in 2002-2003

N = 7760

- Antidepressants: 50
- Mood Stabilizers\(^a\): 25
- Sedatives: 15
- Antipsychotics: 11

\(^a\) Anticonvulsant, 17%; Li, 8%.

Antidepressant-Induced Mania More Common in Bipolar II Compared to Unipolar Depression

Meta-Analysis from Clinical Trials

Unipolar Depression

- TCA = 0.5 (2716)
- SSRI = 0.7 (10,246)
- PBO = 0.2 (3788)

Bipolar II Depression

- TCA > 125
- SSRI > 242
- PBO = 48

N = 125

SSRI = fluoxetine, fluvoxamine, paroxetine, or sertraline.
PBO, placebo; TCA, tricyclic antidepressant.

10-Week Randomized Adjunctive Antidepressants in Acute Bipolar Depression

Response Rates
≥50% IDS Decrease or ≥22 Point CGI-BP Improvement

<table>
<thead>
<tr>
<th></th>
<th>BUP</th>
<th>VEN</th>
<th>SERT</th>
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<tbody>
<tr>
<td>%</td>
<td>49</td>
<td>51</td>
<td>53</td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>65</td>
<td>58</td>
</tr>
<tr>
<td>mg/d</td>
<td>286</td>
<td>195</td>
<td>192</td>
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P = NS

Switch Rates
YMRS > 13

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<tr>
<th></th>
<th>BUP</th>
<th>VEN</th>
<th>SERT</th>
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<tbody>
<tr>
<td>%</td>
<td>4</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>N</td>
<td>51</td>
<td>65</td>
<td>58</td>
</tr>
</tbody>
</table>

NNH
VEN vs BUP 10
VEN vs SERT 13

P = .05

a Absence of placebo group makes efficacy assessment challenging.


BUP, bupropion; CGI-BP, Clinical Global Impression Scale for Bipolar Disorder; IDS, Inventory of Depression Symptomatology; NNH, number needed to harm; SERT, sertraline; VEN, venlafaxine; YMRS, Young Mania Rating Scale.
8-Week Randomized Double-Blind Quetiapine, Paroxetine, and Placebo in Acute Bipolar Depression (EMBOLDEN II)

**MADRS Response**

<table>
<thead>
<tr>
<th></th>
<th>QTP vs PBO</th>
<th>PXT vs PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>NNT</td>
<td>8</td>
<td>46</td>
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</table>

**Somnolence**

<table>
<thead>
<tr>
<th></th>
<th>QTP vs PBO</th>
<th>PXT vs PBO</th>
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<tbody>
<tr>
<td>NNH</td>
<td>6</td>
<td>500</td>
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**Switch Rates**

<table>
<thead>
<tr>
<th></th>
<th>PBO</th>
<th>QTP</th>
<th>PXT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NNH</strong></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>PBO</td>
<td>8.9%</td>
<td></td>
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</tr>
<tr>
<td>QTP</td>
<td>3.1%</td>
<td></td>
<td></td>
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<tr>
<td>PXT</td>
<td>10.7%</td>
<td></td>
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</table>

*P < .01 vs PBO; **P < .0001 vs PBO; ³ QTP = 300-600 mg/d; ⁴ PXT = 20 mg/d.

PXT unapproved for acute bipolar depression.

MADRS, Montgomery-Asberg Depression Rating Scale; NNT, number needed to treat; PXT, paroxetine; QTP, quetiapine.

STEP-BD Randomized Bipolar Depression Studies
NNT for Recovery, Rates

<table>
<thead>
<tr>
<th>Group</th>
<th>NNT</th>
<th>Rate</th>
<th>P-value</th>
</tr>
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<tbody>
<tr>
<td>Mood Stabilizer + Antidepressant</td>
<td>-26</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mood Stabilizer + PBO</td>
<td></td>
<td>23.5%</td>
<td>.40</td>
</tr>
<tr>
<td>Intensive Psychotherapy</td>
<td>8</td>
<td>64.4%</td>
<td>*</td>
</tr>
<tr>
<td>Brief Psychoeducation</td>
<td></td>
<td>51.5%</td>
<td></td>
</tr>
</tbody>
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*P <.05 vs control.

Antidepressants: Adverse Events

- Agitation
- Anxiety
- Sleep disturbances
- Gastrointestinal
- Sexual dysfunction
- May induce switch to hypomania or mania
Conclusions and Recommendations: Role of Antidepressants in Patients With Bipolar Depression

- SSRIs and BUP could be used as first-line treatments in conjunction with mood stabilizer for acute short-term treatment (controversial)
- Caution with the use of VEN because it is associated with increased risk of manic switch
- Antidepressants should not be used for current mixed episode or in patients with history of rapid cycling or antidepressant-induced switching
- Monotherapy with antidepressants NOT recommended for bipolar I
Mood Stabilizers (Lithium; Anticonvulsants) in Bipolar Depression
8-Week Randomized Double-Blind Quetiapine, Lithium, and Placebo in Acute Bipolar Depression (EMBOLDEN I)

### MADRS Response

<table>
<thead>
<tr>
<th></th>
<th>NNT</th>
<th>8</th>
<th>15</th>
<th>NNH</th>
<th>8</th>
<th>20</th>
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<tbody>
<tr>
<td>QTP vs PBO</td>
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<tr>
<td>Li vs PBO</td>
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</table>

### Somnolence

<table>
<thead>
<tr>
<th></th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>QTP vs PBO</td>
<td>8</td>
</tr>
<tr>
<td>Li vs PBO</td>
<td>20</td>
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</table>

### Switch Rates

<table>
<thead>
<tr>
<th></th>
<th>NNH</th>
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</thead>
<tbody>
<tr>
<td>PBO</td>
<td>NNH</td>
</tr>
<tr>
<td>QTP</td>
<td>43</td>
</tr>
<tr>
<td>Li</td>
<td>72</td>
</tr>
</tbody>
</table>

*P < .01 vs PBO; **P < .0001 vs PBO; ^QTP = 300-600 mg/d; ^Li = 0.6 mEq/L. Li unapproved for acute bipolar depression.

Lithium:
Prophylaxis of Bipolar Depression

• Numerous open trials and at least 10 controlled and blind studies support the mood-stabilizing effectiveness of lithium

• Beneficial effects of long-term lithium treatment include reduced depressive episode frequency and duration

Lithium: Rate of Suicidal Acts

- Rates of suicidal acts in Li-treated bipolar patients and general population similar

* Risk-reduction ratio Li vs no Li: 20.7; P < .001.

Lamotrigine in Bipolar Depression

- LTG monotherapy did not show efficacy in the acute treatment of bipolar depression in 4 out of 5 PBO-controlled clinical studies.\(^1\)

- However, a pooled meta-analysis of these 5 studies reported that LTG was superior to PBO in persons with a Hamilton Rating Scale for Depression score of >24 but not in those with score of ≤ 24.\(^2\)

- LTG shows efficacy as maintenance treatment, particularly for delaying recurrence of depression

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Anticonvulsants: Adverse Events

- Metabolic
  - Weight gain
- Neurotoxicity
- Dermatologic
  - Rash
- Safety
  - Stevens-Johnson Syndrome
  - Suicidality
Role of Atypical Antipsychotics in Bipolar Depression
Bipolar I Depression: MADRS Total Score Over 8 Weeks for Aripiprazole or Placebo

Weeks

Baseline

Week 0

PBO (n = 177)

Baseline

ARI (n = 162)

Baseline

PBO (n = 176)

Baseline

ARI (n = 175)

Baseline

Mean Change in MADRS Total Score

Improvement

P = NS at Week 8; *P \leq 0.05; **P \leq 0.01; vs BPO.

ARI, aripiprazole.

ARI unapproved for acute bipolar depression.

Ziprasidone Monotherapy in Acute Bipolar Depression

**Study 1**
Weeks

Mean Change in MADRS

- **ZIP (120-160 mg/d)**
- **ZIP (40-80 mg/d)**
- **PBO**

*P < .05.*
ZIP, ziprasidone.
ZIP unapproved for acute bipolar depression.

Bipolar I Depression: Mood Stabilizer + Ziprasidone

Mean Change in MADRS Score

Weeks

Baseline

ZIP unapproved for acute bipolar depression.
## Overview of Acute Bipolar Depression Studies
### NNT for Response, Rates

<table>
<thead>
<tr>
<th>Approved Treatments</th>
<th>Unapproved Treatments</th>
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<tbody>
<tr>
<td><strong>NNT</strong></td>
<td><strong>NNT</strong></td>
</tr>
<tr>
<td>4 OFC vs PBO</td>
<td>12 OLZ vs PBO</td>
</tr>
<tr>
<td>6 QTP vs PBO</td>
<td>12 LTG vs PBO</td>
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</table>

<table>
<thead>
<tr>
<th>Responder, % (≥50% depression rating decrease)</th>
<th>Responders, %</th>
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<tbody>
<tr>
<td><strong>OFC</strong> Tohen 03</td>
<td><strong>82</strong> 355</td>
</tr>
<tr>
<td><strong>PBO</strong></td>
<td><strong>26</strong> 30</td>
</tr>
<tr>
<td><strong>QTP</strong> Calabrese 05, Thase 06</td>
<td><strong>648</strong> 330</td>
</tr>
<tr>
<td><strong>PBO</strong></td>
<td><strong>59</strong> 19</td>
</tr>
<tr>
<td><strong>OLZ</strong> Tohen 03</td>
<td>351 355</td>
</tr>
<tr>
<td><strong>PBO</strong></td>
<td><strong>39</strong> 9</td>
</tr>
<tr>
<td><strong>LTG</strong> Geddes 09</td>
<td><strong>47</strong> 530</td>
</tr>
<tr>
<td><strong>PBO</strong></td>
<td><strong>9</strong> 38</td>
</tr>
</tbody>
</table>

* P < .05, **P < .01, ***P < .0001 vs PBO.

OFC, olanzapine + fluoxetine; OLZ, olanzapine.

6-Week Randomized Double-Blind Lurasidone Monotherapy in Acute Bipolar I Depression

<table>
<thead>
<tr>
<th></th>
<th>Response Rates</th>
<th>Sedation</th>
<th>≥7% Weight Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>NNT</td>
<td>LUR vs PBO</td>
<td>NNH</td>
</tr>
<tr>
<td>NNT</td>
<td>5</td>
<td></td>
<td>25</td>
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</table>

*P < .0001 vs PBO; LUR = 20-60 or 80-120 mg/d. LUR, lurasidone. LUR unapproved for acute bipolar depression.

Adjunctive Lurasidone in Acute Bipolar I Depression

- PBO + Li or VAL (N = 161)
  - Baseline mean = 30.8
- LUR + Li or VAL (N = 179)
  - Baseline mean = 30.6

LS Mean Change from Baseline

*P = .05; **P = .01; ***P = .001; LS, least squares.
LUR unapproved for acute bipolar depression.
Lurasidone in Bipolar I Depression: Influence of Subsyndromal Hypomanic Symptoms

• All subjects met DSM-IV-TR criteria for bipolar I depression

• The presence or absence of subsyndromal hypomanic symptoms at baseline was defined using YMRS

• Treatment with LUR vs PBO associated with significantly greater reduction in MADRS scores in subjects with and without subsyndromal hypomanic features

LUR unapproved for acute bipolar depression.
# 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>
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<tbody>
<tr>
<td><strong>Metabolic</strong></td>
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<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>
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<tr>
<td>Dyslipidemia</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>0</td>
<td>0</td>
<td>++</td>
<td>++</td>
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<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>
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<tr>
<td><strong>Neurological</strong></td>
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<tr>
<td>Somnolence/sedation</td>
<td>+</td>
<td>0/+</td>
<td>+++</td>
<td>+</td>
<td>0</td>
<td>+++</td>
<td>+++</td>
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<td>EPS</td>
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<td>0/+</td>
<td>+</td>
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<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; RIS, risperidone.

Novel Treatments for Bipolar Depression

- Modafinil/Armodafinil
- Pramipexole
- N-acetyl cysteine
- Ketamine
- Riluzole
- Insulin sensitizers
- Anti-inflammatory agents

All agents unapproved for acute bipolar depression.

8-Week Randomized Double-Blind Adjunctive Armobafinil in Acute Bipolar I Depression

Response Rates
- NNT: 9
- Armobafinil vs PBO: 46.2%
- PBO: 34.2%

AE Discontinuation
- NNH: 50
- Armobafinil vs PBO: 5.6%
- PBO: 3.5%

≥7% Weight Gain
- Armobafinil vs PBO: -2.8%

Patients also taking DVP (24%), LTG (21%), Li (20%), RSP/OLZ (25%), ARI/ZIP (5%)

* P = .015 vs PBO; a 150 mg/d.
Armobafinil unapproved for acute bipolar depression.

Calabrese JR, et al. 51st Annual American College of Neuropsychopharmacology Meeting; Hollywood, FL; December 2-6, 2012. Poster Session III; no. 29.
Pharmacotherapy for Bipolar Depression

- OFC and QTP are FDA approved for bipolar depression
- LUR monotherapy and adjunctive therapy have shown efficacy in bipolar I; LUR has been submitted for FDA approval
- QTP recommended as first-line treatment for bipolar II depression
- ARI and ZIP are not recommended in bipolar depression
- Antidepressants, particularly VEN, are not recommended as monotherapy
- Modafinil and armodafinil have controlled trial data as adjunctive therapy in bipolar I

FDA, US Food and Drug Administration.
Role of Neuromodulation in Bipolar Depression

- ECT (electroconvulsive therapy)\(^1\)
- rTMS (repetitive transcranial magnetic stimulation)\(^2\)
- VNS (vagus nerve stimulation)\(^3\)
- DBS (deep brain stimulation)\(^4\)

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Evidence-Based Psychosocial Treatments for Bipolar Disorder

• Useful in post-acute and maintenance phases of treatment:
  – Cognitive-behavioral therapy
  – Family-focused therapy
  – Interpersonal and social-rhythm therapy
  – Group psychoeducation

• Pharmacotherapy as usual

Combination of Medication and Psychoeducation for Maintenance Treatment in Bipolar Disorder

N = 120

$P < .003$

Bipolar Depression Summary

- Bipolar depression is disabling and frequently misdiagnosed
- Look for probabilistic factors for bipolar depression
- Choose pharmacotherapy with good evidence base as first-line treatment
- Consider safety and tolerability when selecting and sequencing therapy
- Avoid antidepressant monotherapy in bipolar I
- Important role for psychotherapy, including psychoeducation