Pharmacotherapy of Bipolar Disorder

Roger S. McIntyre, MD, FRCPC
Professor of Psychiatry and Pharmacology
University of Toronto
Head, Mood Disorders Psychopharmacology Unit
University Health Network
Toronto, Ontario
Canada
Disclosures

• Advisor/Consultant
  - AstraZeneca Pharmaceuticals LP; Bristol-Myers Squibb Company; Eli Lilly and Company; GlaxoSmithKline; Janssen-Ortho Inc.; Lundbeck, Inc.; Merck & Co., Inc.; Organon Pharmaceuticals USA Inc.; Pfizer Inc; Shire

• Speaker's Bureau

• Research Support
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# 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 symptoms</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>

Diagnosis of Bipolar Disorder Can Be Challenging

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

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

Symptom overlap can lead to misdiagnosis as depressive 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\(^6\)

MDD = major depressive disorder.
\(^1\) Pini et al 2005; \(^2\) Judd et al 2002; \(^3\) Judd et al 2003
Symptom Status in Bipolar Disorder

Bipolar I Disorder

- Asymptomatic: 32%
- Depressed: 53%
- Manic: 9%
- Cycling/Mixed: 6%

Bipolar II Disorder

- Asymptomatic: 46%
- Depressed: 51%
- Manic: 1%
- Cycling/Mixed: 2%

Percentage of Weeks in Affective States During Follow-up

N=146 patients with bipolar I disorder followed for an average of 12.8 years and 86 patients with bipolar II disorder followed for an average of 13.4 years.
Specific DSM-IV Manic Symptoms During an Index Episode of Bipolar Depression in STEP-BD

- No mania (31.2%)
- Subsyndromal mania (54.0%)
- Full mixed episode (14.8%)

Percent of Patients

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

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 physiologic effects of antidepressant

Cumulative Effect of Previous Bipolar Manic Episodes on Neurocognition

Increasing number of manic episodes associated with poorer neurocognition

TMT-A / B, Trail Making Test A / B; WCST, Wisconsin Card Sorting Test.
*p<0.01; **p<0.001 for effect size vs controls.
Effect size >0.70 assumed to be significant.
Bipolar Disorder and Comorbidities: The Rule Rather than the Exception!

- Bipolar Disorder
- Anxiety disorders
- Diabetes mellitus
- Impulse control / suicide
- ADHD
- Personality disorders
- Migraine
- Cardiovascular
- Obesity
- Substance abuse
- Eating disorders
- Anxiety disorders
- Impulse control / suicide


(Somatic comorbidity - green; Psychiatric comorbidity - blue)
Individuals With Bipolar Mania and DSM-5 Defined Mixed Features – More Cardiovascular Disease

Prevalence of cardiovascular disease in patients with pure mania versus mania with MFS

*p<0.05 vs pure mania.
MFS=DSM-5 defined mixed features specifier.
Being Overweight / Obese Has a Negative Effect on Cognitive Function in Euthymic Patients with Bipolar Disorder

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 when compared with normal weight patients with bipolar disorder (p<0.05)

BMI = body mass index.
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)

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

<table>
<thead>
<tr>
<th>Symptoms and Signs</th>
<th>Bipolar Depression Consider more likely if ≥5 are present</th>
<th>Unipolar Depression Consider more likely if ≥4 are present</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Hypersomnia, increased daytime napping</td>
<td>• Initial insomnia, reduced sleep</td>
</tr>
<tr>
<td></td>
<td>• Hyperphagia, increased weight</td>
<td>• Appetite loss and/or weight loss</td>
</tr>
<tr>
<td></td>
<td>• Atypical symptoms (leaden paralysis)</td>
<td>• Normal or increased activity levels</td>
</tr>
<tr>
<td></td>
<td>• Psychotic features, guilt</td>
<td>• Somatic complaints</td>
</tr>
<tr>
<td></td>
<td>• Lability of mood/manic symptoms</td>
<td></td>
</tr>
<tr>
<td></td>
<td>• Rapid onset of depressive symptoms</td>
<td></td>
</tr>
<tr>
<td>Course</td>
<td>• &lt;25 years</td>
<td>• &lt;25 years</td>
</tr>
<tr>
<td></td>
<td>• ≥5 prior major depressive episodes</td>
<td>• Long duration of episode (&gt;6 mo)</td>
</tr>
<tr>
<td>Family history</td>
<td>• Positive for bipolar disorder</td>
<td>• Negative for bipolar disorder</td>
</tr>
</tbody>
</table>
### FDA and EMA-approved Agents for Bipolar Disorder

#### Acute mania

<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>Chlorpromazine</td>
<td>✓</td>
<td>X</td>
</tr>
<tr>
<td>Divalproex (+ ER)</td>
<td>✓</td>
<td>✓&lt;sup&gt;a&lt;/sup&gt;</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>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Carbamazepine ERC</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Asenapine*</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>

#### Acute depression

<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>Quetiapine (+ XR)</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td>Lurasidone*</td>
<td>✓</td>
<td>X</td>
</tr>
</tbody>
</table>

#### Maintenance

<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>✓&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>✓</td>
<td>✓&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Aripiprazole*</td>
<td>✓</td>
<td>✓&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>Quetiapine (+ XR)</td>
<td>✓</td>
<td>✓</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>✓&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Note: licensed indications vary according to market – refer to local Prescribing Information.
Drugs ordered according to year of FDA approval.
*Adjunctive (FDA only) and monotherapy
<sup>a</sup>Treatment of manic episodes when lithium is not tolerated or contraindicated
<sup>b</sup>For prevention of depressive episodes in patients with bipolar I disorder who experience predominantly depressive episodes
<sup>c</sup>For prevention of manic episodes in patients who have responded to acute treatment
<sup>d</sup>Could 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.
Adapted from Ketter & Wang 2010; US Prescribing Information; Irish Summary of Product Characteristics.
### What Clinicians Actually Prescribe for Treatment of Bipolar Disorder

75% of patients had at least two psychotropic drugs for bipolar disorder in the past year

Percentage of patients in the WAVE-bd study who took medication prescribed for bipolar disorder in the past year

<table>
<thead>
<tr>
<th></th>
<th>Bipolar I disorder (%)</th>
<th>Bipolar II disorder (%)</th>
<th>Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>58.2</td>
<td>54.1</td>
<td>56.9</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>39.3</td>
<td>66.4</td>
<td>47.4</td>
</tr>
<tr>
<td>Antiparkinson drugs</td>
<td>3.3</td>
<td>0.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>70.4</td>
<td>53.3</td>
<td>65.1</td>
</tr>
<tr>
<td>Lithium</td>
<td>30.6</td>
<td>17.3</td>
<td>26.5</td>
</tr>
<tr>
<td>Thyroid therapy</td>
<td>1.6</td>
<td>4.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>5.4</td>
<td>4.2</td>
<td>5.0</td>
</tr>
</tbody>
</table>

The Wide AmbispectiveVE study of the clinical management and burden of bipolar disease (WAVE-bd; NCT01062607) study recruited patients from: Austria, Belgium, Brazil, France, Germany, Portugal, Romania, Turkey, Ukraine and Venezuela.

The Needs of Patients with Bipolar Disorder

Aspects of care patients would most like to see improved

- Better treatment of depression
- Lower risk of weight gain
- Prevention of relapse in depression
- Improved functionality / quality of life
- Lower risk of sleeping difficulties
- Lower risk of suicidal thoughts
- Lower risk of diabetes
- Lower risk of muscle stiffness
- Lower risk of sedation

Understanding patients' Needs, Interactions, Treatment, and Expectations (UNITE) global survey of 1300 patients with bipolar disorder. McIntyre, 2009.
## Meta-analysis of Randomized, Controlled, Trials in Acute Mania

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hedges’s g</th>
<th>Lower limit</th>
<th>Upper limit</th>
<th>p-Value</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tamoxifen</td>
<td>2.32</td>
<td>1.67</td>
<td>2.96</td>
<td>0.000</td>
<td>74</td>
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<tr>
<td>Risperidone</td>
<td>0.66</td>
<td>0.45</td>
<td>0.88</td>
<td>0.000</td>
<td>823</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>0.61</td>
<td>0.32</td>
<td>0.89</td>
<td>0.000</td>
<td>427</td>
</tr>
<tr>
<td>Haloperidol</td>
<td>0.54</td>
<td>0.35</td>
<td>0.73</td>
<td>0.000</td>
<td>1051</td>
</tr>
<tr>
<td>Cariprazine</td>
<td>0.51</td>
<td>0.13</td>
<td>0.89</td>
<td>0.009</td>
<td>235</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>0.46</td>
<td>0.29</td>
<td>0.62</td>
<td>0.000</td>
<td>1335</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>0.42</td>
<td>0.19</td>
<td>0.66</td>
<td>0.000</td>
<td>663</td>
</tr>
<tr>
<td>Asenapine</td>
<td>0.40</td>
<td>0.13</td>
<td>0.66</td>
<td>0.003</td>
<td>569</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>0.40</td>
<td>0.20</td>
<td>0.59</td>
<td>0.000</td>
<td>1007</td>
</tr>
<tr>
<td>Lithium</td>
<td>0.39</td>
<td>0.22</td>
<td>0.55</td>
<td>0.000</td>
<td>1199</td>
</tr>
<tr>
<td>Paliperidone</td>
<td>0.30</td>
<td>0.11</td>
<td>0.49</td>
<td>0.002</td>
<td>1001</td>
</tr>
<tr>
<td>Valproate</td>
<td>0.28</td>
<td>0.09</td>
<td>0.47</td>
<td>0.003</td>
<td>1046</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>0.26</td>
<td>0.10</td>
<td>0.41</td>
<td>0.001</td>
<td>1662</td>
</tr>
<tr>
<td>Licarbazepine</td>
<td>0.09</td>
<td>-0.27</td>
<td>0.45</td>
<td>0.621</td>
<td>313</td>
</tr>
<tr>
<td>Verapamil</td>
<td>-0.02</td>
<td>-0.86</td>
<td>0.83</td>
<td>0.970</td>
<td>20</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>-0.02</td>
<td>-0.43</td>
<td>0.39</td>
<td>0.927</td>
<td>179</td>
</tr>
<tr>
<td>Topiramate</td>
<td>-0.06</td>
<td>-0.25</td>
<td>0.13</td>
<td>0.508</td>
<td>1074</td>
</tr>
</tbody>
</table>

**Figure 1** Forest plot of Hedges’ $g$ with its 95% upper and lower limits (confidence interval (CI)), based on mania score changes in 55 drug/placebo comparisons, based on random effects meta-analysis. Filled squares indicate pooled results of individual drugs (and their CI). Drugs are listed according to the magnitude of the pooled effect sizes (Hedges’ $g$).
Randomized, double-blind, placebo-controlled study of divalproex extended release loading monotherapy in ambulatory bipolar spectrum disorder patients with moderate-to-severe hypomania or mild mania.

The mean rate of change for the divalproex ER group, estimated by random-effects regression, was significantly greater than for the placebo group (P = .024).
Lamotrigine in Bipolar Depression

Role of Intraneuronal Aspartate

Lamotrigine is not approved by the US FDA for bipolar depression.

Cho, choline-containing compounds; Cr, creatine + phosphocreatine; Glx, glutamate + glutamine; ml, myo-inositol; NAA, N-acetylaspartate.

T1-weighted sagittal magnetic resonance imaging location for anterior cingulate/medial prefrontal cortex single-voxel, water-suppressed (Haase 1985) PRESS (Bottomley 1987); 1H-MRS (TR/TE=3 s/30 ms; number of averages=256; voxel size=3x3x3 cm^3).


Lamotrigine in Bipolar Depression

- Lamotrigine monotherapy did not show efficacy in the acute treatment of bipolar depression in 4 out of 5 placebo-controlled clinical studies.\(^1\)
- However, an individual patient data meta-analysis of these same studies reported that lamotrigine was superior to placebo in people with a Hamilton Rating Scale for Depression score of >24 but not in those of score of \(\leq 24\).\(^2\)
- Lamotrigine shows efficacy as maintenance treatment.

High-Dose Levothyroxine (T4) May Decrease Bipolar Depression in Women

Placebo (n=16) Levothyroxine (n=14)

Placebo (n=15) Levothyroxine (n=17)

HAMD$_{17}$, 17-Item Hamilton Depression Rating Scale.

Mean levothyroxine dose, 300 µg. Hypothyroidism is 6-7x more common in women than in men.


*P<0.05. 0.81 when age adjusted

Levothyroxine is not approved by the US FDA for bipolar depression.
Bipolar I Depression: MADRS Total Score over 8 Weeks for Olanzapine, OFC or Placebo

Mean change in MADRS total score

Bipolar Depression:
MADRS Total Score over 8 Weeks For Quetiapine vs Placebo

BOLDER I & II and EMBOLDEN I & II pooled data

Time (weeks)

0 1 2 3 4 5 6 7 8

Mean change in MADRS total score

-20.00 -15.00 -10.00 -5.00 0.00

Quetiapine 300 mg/day (n=811)

***p<0.001 vs placebo (ITT; LOCF)
Lurasidone Monotherapy for Bipolar Depression

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

![Graph showing change in MADRS from baseline](image)

- Change in MADRS from Baseline
- \( d = 0.45 \)
- \( d = 0.45 \)
- \( d = 0.45 \)

Add-on Lurasidone for Bipolar Depression

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

Change in MADRS from Baseline

-17.1

-13.5

Lurasidone (n=183)  Placebo (n=165)

MMRM: $P < .01$.

MMRM = mixed-effect model repeated measure

Lurasidone Efficacious in Bipolar Depression with Subsyndromal Hypomania


**P < .01.**

MADRS Responder Rate (LOCF-endpoint) (%)

<table>
<thead>
<tr>
<th>Subsyndromal Hypomania Group 1</th>
<th>Subsyndromal Hypomania Group 2</th>
<th>No Subsyndromal Hypomania</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lurasidone</td>
<td>Placebo</td>
<td>Lurasidone</td>
</tr>
<tr>
<td>51.1</td>
<td>32.2</td>
<td>53.2</td>
</tr>
<tr>
<td>Placebo</td>
<td>Lurasidone</td>
<td>Placebo</td>
</tr>
<tr>
<td>51.1</td>
<td>31.1</td>
<td>27.8</td>
</tr>
</tbody>
</table>

**P < .01.**
Long-term Treatment With Lurasidone

Open-label Extension Study in Bipolar I Depression

Mean Change From DB Baseline

MADRS Total Score, DB Baseline to OL Baseline

DB Baseline
OL Baseline
Month 1
Month 2
Month 3
Month 4
Month 5
Month 6

Prior ADJ-LUR (n=254)
Prior MONO-LUR (n=210)
Prior ADJ-PBO (n=243)
Prior MONO-PBO (n=106)

Completed extension (n):
173
151
161
74

ADJ, adjunctive; DB, double-blind; LUR, lurasidone; OC, observed cases; OL, open-label; PBO, placebo.
OL dosing: 60 mg x 1 week, flexible dosing thereafter for an additional 24 weeks.
Assignments during one of the preceding 6-week, randomized, double-blind treatment studies
# Mood Stabilizers: Safety and Tolerability

<table>
<thead>
<tr>
<th></th>
<th>Lithium</th>
<th>Valproate</th>
<th>Carbamazepine</th>
<th>Lamotrigine</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastrointestinal</strong></td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
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<tr>
<td>Weight gain</td>
<td>Weight gain</td>
<td>Weight gain</td>
<td>Rash</td>
<td>Rash</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Neurotoxicity</td>
<td>Neurotoxicity</td>
<td>Headache</td>
<td>Headache</td>
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<tr>
<td>Renal toxicity</td>
<td>Renal toxicity</td>
<td>Renal toxicity</td>
<td>Hepatotoxicity</td>
<td>Hepatotoxicity</td>
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<tr>
<td>Thyroid toxicity</td>
<td>Thyroid toxicity</td>
<td>Thyroid toxicity</td>
<td>Thyroid changes</td>
<td>Thyroid changes</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>Hair Loss</td>
<td>Hair Loss</td>
<td>Abnormal dreams</td>
<td>Abnormal dreams</td>
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<tr>
<td>Cardiac toxicity</td>
<td>Cardiac toxicity</td>
<td>Cardiac toxicity</td>
<td>Cardiac toxicity</td>
<td>Cardiac toxicity</td>
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<tr>
<td>Acne, Psoriasis</td>
<td>Acne, Psoriasis</td>
<td>Acne, Psoriasis</td>
<td>PCOS</td>
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<tr>
<td>Teratogen</td>
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<td>Teratogen</td>
<td>Teratogen</td>
<td>Teratogen</td>
</tr>
<tr>
<td>Suicidality (?)</td>
<td>Suicidality (?)</td>
<td>Suicidality (?)</td>
<td>Suicidality (?)</td>
<td>Suicidality (?)</td>
</tr>
</tbody>
</table>

*boxed warning in prescribing information; (?)=recent alert.*

All mood stabilizers have at least one boxed warning.

PCOS = polycystic ovarian syndrome.
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>
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</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.
# NNT/NNH With Antipsychotics for Acute Bipolar Depression

**Table:**

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>NNT</th>
<th>NNH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Olanzapine/Fluoxetine</td>
<td>4 (response) 5 (remission)</td>
<td>7 (weight gain) 9 (diarrhea) 6 (weight gain &gt;7% from baseline)</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>6</td>
<td>5 (sedation)</td>
</tr>
<tr>
<td>Lurasidone</td>
<td>5</td>
<td>17 (nausea) 15 (akathisia) 25 (sedation) -493 (weight gain)</td>
</tr>
</tbody>
</table>

NNT, number needed to treat; NNH, number needed to harm.
# Metabolic Risk of Select Treatments for Bipolar Depression

<table>
<thead>
<tr>
<th>Medication</th>
<th>Weight</th>
<th>Dyslipidemia</th>
<th>Blood Pressure</th>
<th>Glucose Level</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mood Stabilizers</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lithium&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>• Valproate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑</td>
<td>Inconsistent findings</td>
<td>↔</td>
<td>↔ (due to hyperinsulinemia)</td>
</tr>
<tr>
<td>• Lamotrigine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>• Carbamazepine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↔</td>
<td>↑</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td><strong>Antipsychotics</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lurasidone</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>• Olanzapine&lt;sup&gt;a&lt;/sup&gt;</td>
<td>↑↑↑</td>
<td>↑↑↑</td>
<td>↔</td>
<td>↑</td>
</tr>
<tr>
<td>• Quetiapine</td>
<td>↑</td>
<td>↑</td>
<td>↔</td>
<td>Inconsistent findings</td>
</tr>
</tbody>
</table>

## Antidepressant Use in Bipolar Disorder: The ISBD Task Force Consensus Report

<table>
<thead>
<tr>
<th>Domain</th>
<th>Recommendation</th>
</tr>
</thead>
</table>
| **Acute treatment**  | 1. Adjunctive antidepressants may be used for an acute bipolar I or II depressive episode when there is a history of previous positive response to antidepressants  
                        2. Adjunctive antidepressants should be avoided for an acute bipolar I or II depressive episode with two or more concomitant core manic symptoms, in the presence of psychomotor agitation or rapid cycling |
| **Maintenance treatment** | 3. Maintenance treatment with adjunctive antidepressants may be considered if a patient relapses into a depressive episode after stopping antidepressant therapy |
| **Monotherapy**      | 4. Antidepressant monotherapy should be avoided in bipolar I disorder  
                        5. Antidepressant monotherapy should be avoided in bipolar I and II depression with two or more concomitant core manic symptoms |

Recommendation statements only shown for acute treatment, maintenance treatment and monotherapy (12 in total); each statement included in the recommendations was rated by at least 80% of ISBD experts as ‘essential’ or ‘important’

Risk Factors 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.
Novel Treatments for Bipolar Depression

- Modafinil
- Pramipexole
- N-acetyl cysteine
- Ketamine
- Riluzole
- Insulin sensitizers
- Anti-inflammatory
Adjunctive Lisdexamfetamine Benefits ADHD Symptom Severity and Metabolic Parameters in Stable Bipolar Disorder

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

† p<0.001 vs baseline

Lisdexamfetamine (n=40)
Modafinil or Armodafinil in Bipolar Depression

Adjunctive Modafinil\textsuperscript{c,e} vs Placebo\textsuperscript{1}

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
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<tbody>
<tr>
<td>Score</td>
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<td></td>
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</tr>
<tr>
<td>Modafinil (n=41)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Placebo (n=44)</td>
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<td></td>
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<td></td>
</tr>
</tbody>
</table>

Adjunctive Armodafinil\textsuperscript{d,e} vs Placebo\textsuperscript{2}

<table>
<thead>
<tr>
<th>Week</th>
<th>Baseline</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>7</th>
<th>8</th>
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<tbody>
<tr>
<td>Score</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Armodafinil 150 mg (n=201)</td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
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<tr>
<td>Placebo (n=199)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

1 positive “proof of concept” trial

\textsuperscript{a}P<0.01; \textsuperscript{b}P\leq0.05; \textsuperscript{c}Adjunctive to mood stabilizers or antidepressants; \textsuperscript{d}Adjunctive to mood stabilizers; \textsuperscript{e}Modafinil and armodafinil are not approved by the US FDA for bipolar depression.

IDS, Inventory of Depressive Symptomatology; IDS-C\textsubscript{30}, 30-item IDS–Clinician-Rated.


Novel spectrum of efficacy:

- 1 positive Phase 3 trial
- 2 negative/failed Phase 3 trials
- Concentration/decision making
- Energy/fatigability
- Leaden paralysis/physical energy
- Increased appetite
Ketamine in Acute Bipolar Depression

Robust Transient Efficacy with Single Infusion

Ketamine is not approved by the US FDA for bipolar depression.

N=15 subjects with bipolar I or II depression on therapeutic levels of lithium or valproate received a single intravenous infusion of either ketamine (0.5 mg/kg) or placebo on 2 test days 2 weeks apart.


$^{a} p<0.001; ^{b} p<0.05$ kétamine vs placebo.
NAC in Bipolar Depression
Adjunctive Maintenance Treatment

Mean Score at Endpoint

<table>
<thead>
<tr>
<th>Scale</th>
<th>NAC (n=10)</th>
<th>Placebo (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MADRS</td>
<td>9.60</td>
<td>11.20</td>
</tr>
<tr>
<td>BDRS</td>
<td>23.57</td>
<td>19.86</td>
</tr>
<tr>
<td>YMRS</td>
<td>4.40</td>
<td>2.71</td>
</tr>
<tr>
<td>GAF</td>
<td>62.70</td>
<td>53.00</td>
</tr>
<tr>
<td>RIFT</td>
<td>10.50</td>
<td>15.86</td>
</tr>
<tr>
<td>Q-LES-Q</td>
<td>53.40</td>
<td>43.29</td>
</tr>
</tbody>
</table>

Effect size measured using Hedge’s g.
NAC is not approved by the US FDA for bipolar depression.
BDRS, Bipolar Depression Rating Scale; GAF, Global Assessment of Functioning; RIFT, Range of Impairment Functioning Tool; Q-LES-Q, Quality of Life Enjoyment and Satisfaction Questionnaire.
PPAR-γ Agonism in Bipolar Depression
Proof-of-Concept Open Label Trial of Pioglitazone

Mean Scores

P < 0.001 for change at 8 weeks for all parameters.
Pioglitazone is not approved by the US FDA for bipolar depression.
N = 34 patients with bipolar disorder (I, II, or not otherwise specified) and metabolic syndrome/insulin resistance who were currently depressed (QIDS total score ≥ 11) despite a mood stabilizer; pioglitazone dose: 15-30 mg/day for 8 weeks.
PPAR, peroxisome proliferator-activated receptor; QIDS, Quick Inventory of Depressive Symptomatology; SIGH-A, Structured Interview Guide for the Hamilton Anxiety rating scale.
When to Use ECT or Experimental Treatments

- Rapid response to severe symptoms needed
- Acute episode is not responding on time to ‘optimal’ treatment
- Proven treatment(s) not tolerable or safe
- Breakthrough episode despite ‘optimal’ maintenance
- Maintenance treatment is intolerable or unsafe
FIGURE 2. Change in Depression Severity in Patients With Treatment-Resistant Bipolar Depression Randomly Assigned to ECT or Algorithm-Based Pharmacological Therapy

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).
Deep Brain Stimulation in Treatment-Resistant Unipolar and Bipolar Depression
Marked Improved Associated With Subcallosal Cingulate

- Single-blind sham stimulation followed by 24-week open-label active stimulation
- N=17 (10 women)
  - 10 with unipolar and 7 with bipolar depression
  - Mean duration index episode: 64 months
  - Nonresponse to an average of 6.2 prior antidepressants
- Response
  - 41% at 24 weeks\(^a\)
  - 92% at 2 years
- Remission
  - 18% at 24 weeks\(^a\)
  - 58% at 2 years
- Discontinuation recurrence: 3/3 (100%)
- No significant differences (unipolar vs bipolar) at any point

\(^a\)Primary outcome.
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.

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.
# Treatment of Acute Bipolar - Depression

**LEVEL 3 – If levels 1 and 2 are ineffective or treatment not tolerated**
- Electroconvulsive therapy (ECT)

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

**LEVEL 4 – If levels 1-3 are ineffective or treatment 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, armodafinial, or omega-3 fatty acids for bipolar depression.
Managing Bipolar Maintenance
Correlation Between Residual Manic Symptoms and Time to Recurrence

**Time to Depressive Recurrence**

- Cumulative proportion without recurrence
  - Time to depressive recurrence (weeks)
  - N = 156: 46, 16, 2
  - N = 702: 309, 164, 19
  - Total N = 858: 355, 180, 21

**Time to Manic Recurrence**

- Cumulative proportion without recurrence
  - Time to manic recurrence (weeks)
  - N = 156: 46, 16, 2
  - N = 702: 309, 164, 19
  - Total N = 858: 355, 180, 21

STEP-BD trial
Lithium Plus Valproate vs Monotherapy for Relapse Prevention in Bipolar I Disorder

Randomized, open-label trial

\[ P = 0.0023 \text{ for combination (n=110) vs valproate (n=110); } P = 0.27 \text{ for combination vs lithium (n=110); } P = 0.472 \text{ for lithium vs valproate} \]

Long-term Outcome in Bipolar Depression: Lamotrigine Adjunct to Lithium with the Possibility of the Addition of Paroxetine

- Median time to relapse: 10.0 months (95% CI: 1.1–18.8) for Lamotrigine (n=64)
- Median time to relapse: 3.5 months (95% CI: 0.7–7.0) for Placebo (n=60)

Double-blind, randomized trial
Stage of Illness and Treatment Response in Bipolar Disorder

**Mania**

- Probability of first relapse to mania over time from first symptomatic remission of mania (weeks).

**Depression**

- Probability of first relapse to depression over time from first symptomatic remission of depression (weeks).

*Pooled data from randomised, double-blind trials*  
Multi-episode Illness Associated with Decreased Treatment Responsiveness in Patients with Bipolar Disorder

![Graph showing the relationship between number of previous episodes and patients with recurrence.]

- Cognitive-behavioural therapy (n=127)
- Usual treatment (n=126)

Randomised trial.
## Self-management Strategies for Bipolar Disorder

<table>
<thead>
<tr>
<th>Psychosocial Goals and Recommended Approaches</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adherence to Medication</strong></td>
</tr>
<tr>
<td>• Improve adherence via close monitoring and collaborative relationship</td>
</tr>
<tr>
<td>• Titrate medications appropriately to improve efficacy and minimize adverse events</td>
</tr>
<tr>
<td><strong>Education on Bipolar Disorder</strong></td>
</tr>
<tr>
<td>• Provide easily accessible, high-quality disease state information</td>
</tr>
<tr>
<td>• Consider books, Internet, and support groups</td>
</tr>
<tr>
<td><strong>Regular Sleep/Wake Cycles</strong></td>
</tr>
<tr>
<td>• Emphasize sleep hygiene as part of larger strategy for exercise, rest, and diet</td>
</tr>
<tr>
<td><strong>Reduction in Dysfunctional Attitudes</strong></td>
</tr>
<tr>
<td>• Convey compassion, positive self-talk, and positive projecting</td>
</tr>
<tr>
<td><strong>Family Communication</strong></td>
</tr>
<tr>
<td>• Include family members in monitoring and evaluations of social interactions</td>
</tr>
<tr>
<td><strong>Early Recognition of Prodromes</strong></td>
</tr>
<tr>
<td>• Emphasize proactive responses and prevention plans in anticipation of manic or depressive phases</td>
</tr>
<tr>
<td>• Suggest “mindfulness” strategy</td>
</tr>
</tbody>
</table>

Conclusion

• Employ probabilistic approach to bipolar disorder
• Comorbidity common, hazardous and moderates outcome in bipolar
• Acute mania treatments differentiate on tolerability/safety; atypical antipsychotics faster onset of action vs. lithium
• Acute bipolar depression options significantly different on tolerability/safety, e.g., weight-gain liability, metabolic disruption
• Adjunctive psychosocial treatments significantly improve outcome
• Neuromodulatory treatments highly effective