Managing Bipolar Depression and Mixed Episodes
Outline

- Diagnosing bipolar disorder with DSM-5
- Treating mixed features of bipolar disorder
- Improving health outcomes in bipolar depression
- Role of psychosocial treatments in bipolar patients
**Diagnosis of Bipolar Disorder Can Be Challenging**

<table>
<thead>
<tr>
<th>Summary</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Initial diagnosis can take ≥10 years</strong></td>
</tr>
<tr>
<td><strong>Patients with bipolar disorder more likely to present with symptoms of depression</strong></td>
</tr>
<tr>
<td><strong>Symptom overlap can lead to misdiagnosis as depressive symptoms are difficult to distinguish from MDD</strong></td>
</tr>
<tr>
<td><strong>One-third of patients are misdiagnosed with MDD</strong></td>
</tr>
<tr>
<td><strong>Comorbidities (eg anxiety disorder, alcohol and substance abuse, cognitive or attention disorders, eating disorders) are common and complicate diagnosis</strong></td>
</tr>
</tbody>
</table>

MDD = major depressive disorder.
Bipolar and Related Disorders

Changes from DSM-IV:
• Formerly listed under Mood Disorders
• Abnormally and persistently increased goal-directed activity or energy added as a core symptom of manic and hypomanic episodes
• Mixed Episodes removed and replaced with: “With Mixed Features,” which can be applied to the current manic, hypomanic, or depressive episode in bipolar I or II

• Bipolar I disorder
• Bipolar II disorder
• Cyclothymic disorder
• Substance/medication-induced bipolar and related disorder
• Bipolar and related disorder due to another medical condition

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

**Core symptoms**
- Manic
- Depressive

**Elevated mood**
- DSM-IV-TR: Elevated mood
- DSM-5: Elevated mood + energy

**Depressed mood or loss of interest**
- DSM-IV-TR: Depressed mood or loss of interest
- DSM-5: Depressed mood or loss of interest with mixed features

**DSM-IV-TR**
- Manic
- Mixed
- Depressive

**DSM-5**
- Manic
- Hypomanic/Manic with mixed features
- Depressive with mixed features
- Depressive

Bipolar Specifiers

• With anxious distress:
  – Feeling keyed up or tense
  – Difficulty concentrating because of worry
  – Fear that individuals 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

Jail/Prison Has Replaced State Hospitals

Mania is an Emergency

- Need rapid, safe stabilization
- Reduction of behavioral agitation
- Sleep restoration and management of withdrawal from drugs and alcohol
- Antimanic treatment based on
  - Manic episode (mixed vs manic)
  - Rapid cycling or psychotic symptoms
  - Patient’s medication history
  - Presence of comorbidities
  - Willingness to accept therapy
Goal of Treatment: Mood Stabilization

Mood stabilizers

- Acute treatment or stabilization of manic/mixed, hypomanic, and depressive episodes
- Do not induce alternate mood symptoms (i.e., switch)
- Prevent future relapse or recurrence of manic/mixed, hypomanic, or depressive symptoms or episodes

“More lithium.”
What Clinicians Actually Prescribe for Treatment of Bipolar Disorder

75% of patients had at least two psychototropic 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>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>58</td>
<td>54</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>39</td>
<td>66</td>
</tr>
<tr>
<td>Antiparkinson drugs</td>
<td>3</td>
<td>0.3</td>
</tr>
<tr>
<td>Antipsychotic drugs</td>
<td>70</td>
<td>53</td>
</tr>
<tr>
<td>Lithium</td>
<td>31</td>
<td>17</td>
</tr>
<tr>
<td>Thyroid therapy</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>4</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. WAVE-bd, Study of the Clinical Management of Bipolar Disease. Vieta, et al. 2011.
## FDA Approved Bipolar Disorder Treatments*

<table>
<thead>
<tr>
<th>Agent</th>
<th>Manic</th>
<th>Mixed</th>
<th>Depression</th>
<th>Maintenance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aripiprazole</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Asenapine</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Paliperidone-ER</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</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Olanzapine/Fluoxetine</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Quetiapine/XR</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Risperidone (Oral/IM)</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+ (IM)</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Chlorpromazine</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Carbamazepine ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Divalproex DR/ER</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Lithium</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

*Aripiprazole, asenapine, olanzapine, quetiapine, risperidone indication as monotherapy and adjunct to Li or DVPX and with/without psychosis.
Mania score changes in 55 drug/placebo comparisons, based on random effects meta-analysis.
Cipriani Meta Analysis

Aim
Evaluate comparative effects of all antimanic drugs

Methods
Multiple treatments meta-analysis (accounts for direct and indirect comparisons)

Sample
68 RCTs
Jan 1, 1980–Nov 25, 2010
16,073 subjects
All comparisons ITT population

ARI=aripiprazole, ASE=asenapine, CBZ=carbamazepine, VAL=valproate, GBT=gabapentin, HAL=haloperidol, LAM=lamotrigine, LIT=lithium, OLZ=olanzapine, PBO=placebo, QTP=quetiapine, RIS=risperidone, TOP=topiramate, ZIP=ziprasidone

Adapted from Lancet 2011; doi:10.1016/S0140-6736(11)60873-8
## Variable Lithium Response Rate

Based on Bipolar Subtype

<table>
<thead>
<tr>
<th>Poor Response 30%</th>
<th>Poor Response 70%</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rapid Cycling</strong></td>
<td><strong>Nonrapid Cycling</strong></td>
</tr>
<tr>
<td>Mixed Mania</td>
<td>Euphoric Mania</td>
</tr>
<tr>
<td>Substance Abuse</td>
<td>No Substance Abuse</td>
</tr>
<tr>
<td>(-) Family History</td>
<td>(+) Family History</td>
</tr>
<tr>
<td>&gt;3 Episodes</td>
<td>Few Lifetime Episodes</td>
</tr>
<tr>
<td>DMI Pattern</td>
<td>MDI Pattern</td>
</tr>
</tbody>
</table>

- **DMI** = Depression and Mania Inventory
- **MDI** = Mania and Depression Inventory

Atypical Antipsychotics in Acute Mania

Pros
• As a class, effective in acute mania
• Rapid control of acute mania/mixed, rapid cycling, psychosis/no psychosis
• Sustained improvement of symptoms

Cons
• Tardive dyskinesia, neuroleptic malignant syndrome
• Weight gain

TD=tardive dyskinesia; EPS=extrapyramidal symptoms.
Cariprazine in Patient With Acute Mania Associated with Bipolar I Disorder


Not FDA approved for mania.
Cariprazine in Patients With Acute Mania Associated with Bipolar I Disorder

Mean dose 7.5mg/day

Not FDA approved for mania.
Sachs GS et al. J Affective Dis. 2015
Actavis and Gedeon Richter Announce FDA Receipt of NDA Resubmission for Cariprazine

- Potential Treatment of Both Schizophrenia and Manic or Mixed Episodes Associated with Bipolar I Disorder - DUBLIN and BUDAPEST, Hungary, Jan. 6, 2015 /PRNewswire/

-- Actavis plc (NYSE: ACT) and...
- Potential Treatment of Both Schizophrenia and Manic or Mixed Episodes Associated with Bipolar I Disorder -

DUBLIN and BUDAPEST, Hungary, Jan. 6, 2015 /PRNewswire/ -- Actavis plc (NYSE: ACT) and Gedeon Richter Plc. today announced that the U.S. Food and Drug Administration (FDA) has acknowledged receipt of Actavis' New Drug Application (NDA) resubmission for its atypical antipsychotic cariprazine, a potent dopamine D3/D2 receptor partial agonist with preferential binding to D3 receptors. The Prescription Drug User Fee Act (PDUFA) date is expected to be in the second quarter of 2015.
Typical Antipsychotics in Acute Mania

Pros

• Efficacious for acute mania
• Haloperidol more efficacious than olanzapine, quetiapine, ziprasidone

Cons/adverse effects

• Acute EPS, TD, akathisia, NMS

Negative impact on course of illness

• ↑ post manic depressive symptom severity
• ↑ frequency of major depressive episodes

Vieta et al. 2010.
Anticonvulsants in Acute Mania

Pros

• Effective in manic and mixed episodes
• Effective in alcohol withdrawal and relapse prevention
• Several effective in migraine prevention

Cons

• Ineffective in acute mania (LTG, TPX, GBP)
• P450 3A4 heteroinduction
• Weight gain and endocrine disturbances (VAL)
• Teratogenicity (VAL, CBZ)
• Rash risk

CBZ=carbamazepine; VAL=valproate; LTG=lamotrigine; GBP=gabapentin; OLZ=olanzapine; DVPX=divalproex; TPX=topiramate
ECT for Acute Mania

• Electroconvulsive therapy (ECT) is a mood stabilizer
• 2 controlled studies of acute mania
  – ECT vs lithium
  – ECT vs lithium + haloperidol
• ECT reported significant benefits for acute mania

# Target Dose Range for Acute Mania/Mixed

<table>
<thead>
<tr>
<th>AGENT</th>
<th>MONO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lithium</td>
<td>0.8–1.2 mmol/L</td>
</tr>
<tr>
<td>Divalproex</td>
<td>90–125 mg/L</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>4–12 mcg/ml vs 800 mg</td>
</tr>
<tr>
<td>Asenapine</td>
<td>10 mg BID sublingual</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>10–20 mg/day</td>
</tr>
<tr>
<td>Risperidone</td>
<td>4–5 mg/day</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>600–800 mg/day</td>
</tr>
<tr>
<td>Ziprasidone</td>
<td>80–120 mg/day</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>15–30 mg/day</td>
</tr>
<tr>
<td>Clozapine</td>
<td>150–450 mg</td>
</tr>
<tr>
<td>Mood Stabilizer Safety and Tolerability Concerns</td>
<td></td>
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<tr>
<td>-----------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Lithium</strong></td>
<td><strong>Valproate</strong></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Weight gain</td>
<td>Weight gain</td>
</tr>
<tr>
<td>Neurotoxicity</td>
<td>Tremor</td>
</tr>
<tr>
<td>Renal toxicity</td>
<td>Hepatotoxicity</td>
</tr>
<tr>
<td>Thyroid toxicity</td>
<td>Thrombocytopenia</td>
</tr>
<tr>
<td>Hair Loss</td>
<td>Hair Loss</td>
</tr>
<tr>
<td>Cardiac toxicity</td>
<td>Pancreatitis</td>
</tr>
<tr>
<td>Acne, Psoriasis</td>
<td>PCOS</td>
</tr>
<tr>
<td>Teratogen</td>
<td>Teratogen</td>
</tr>
<tr>
<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

Mania/Mixed Episodes Matter

• Treat the illness
  – Short-term high-dose benzodiazepine, sleep restoration, containment

• Individualize treatment
  – Right medication to the right patient

• Improved psychoeducation

• Enhanced treatment adherence and minimize side-effect burden
Depressed State is Much More Frequent in Bipolar Patients than Hypomania

NIMH Collaborative Depression Study: 13-year follow-up of 146 bipolar patients

- Hypomanic: 9%
- Depression & Mixed States: 38%
- Asymptomatic: 53%

Judd LL et al. Arch Gen Psychiatry. 2002;59:530-537.
# Probabilistic Approach to Bipolar Depression

*Bipolar I Depression more likely if ≥5:*

<table>
<thead>
<tr>
<th><strong>Symptomatology</strong></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersomnia</td>
<td></td>
</tr>
<tr>
<td>Hyperphagia</td>
<td></td>
</tr>
<tr>
<td>Psychomotor retardation</td>
<td></td>
</tr>
<tr>
<td>Other “atypical” symptoms</td>
<td></td>
</tr>
<tr>
<td>Psychosis and/or pathological guilt (OR=3.3)</td>
<td></td>
</tr>
</tbody>
</table>

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

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

Progression to Bipolar Disorder from MDD with Subthreshold Hypomania

N=550 individuals followed for >1 year (mean follow-up, 17.5 years) after a diagnosis of major depression at intake

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

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

Percent of Patients

Number of DSM-IV Manic Symptoms

Baseline Manic Symptom Severity in Depression Prior to Antidepressant Treatment

**YMRS Score**

TEM (n=44)  ADNR (n=44)  ADR (n=84)

*F(2,169)=4.5; P<0.01

**CGI Severity Mania**

TEM (n=44)  ADNR (n=494)  ADR (n=84)

†F(2,169)=3.4; P=0.04

TEM=treatment-emergent mania; ADR=antidepressant responder; ADNR=antidepressant nonresponder.

Increased Rates of Metabolic Syndrome in Bipolar Disorder: an International Observation

NHANES III – prevalence of NCEP III-defined metabolic syndrome in general population: 23.7%

Estimates of metabolic syndrome in bipolar disorder population: 20%–66%

NHANES III=Third National Health and Nutrition Examination Survey.
NCEP III=National Cholesterol Education Program Adult Treatment Protocol.
McIntyre et al. 2010.
Phenotype

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
The Needs of Patients with Bipolar Disorder

Understanding patients' Needs, Interactions, Treatment, and Expectations (UNITE) global survey of 1300 patients with bipolar disorder. McIntyre 2009.

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

Respondents (%)

Prevention of relapse in depression
Improved functionality/quality of life
Lower risk of weight gain
Better treatment of depression
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.
MADRS Response Rates Across Six Lamotrigine Acute Bipolar Depression Studies

Response: ≥50% improvement over baseline. Pooled relative risk of response: 1.22; confidence interval (CI) 1.06, 1.41; P=0.005. MADRS=Montgomery Åsberg Depression Rating Scale.

Bipolar I Depression: MADRS Total Score Over 8 Weeks for Olanzapine, OFC, or Placebo

LSM Change in MADRS Total Score

Time (weeks)

Placebo (n=355)
Olanzapine (n=351)
OFC (n=82)

*p<0.001 vs placebo for olanzapine and OFC.
†p<0.05 vs olanzapine for OFC (ITT; MMRM).
Tohen et al. 2003.
Bipolar Depression: MADRS Total Score Over 8 Weeks for Quetiapine Vs Placebo

BOLDER I & II and EMBOLDEN I & II Pooled Data

***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

\[ d = 0.45 \]

Change in MADRS from Baseline

- 20-60 mg (n=166)*: -15.4
- 80-120 mg (n=160)†: -15.4
- Placebo (n=170): -10.7

Add-on Lurasidone for Bipolar Depression

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

Lurasidone Efficacious in Bipolar Depression with Subsyndromal Hypomania

Lurasidone for Mixed Depression
RESOLVE Study

- 211 MDD patients with 2 or 3 manic symptoms
- Lurasidone 20-60mg/day or placebo (mean 36.2 mg/day)
- MADRS primary efficacy measure
- CGI-S, YMRS, HAM-A secondary efficacy measures
- NNT was 3 and 4 for response and remission resp.
- Lurasidone better than placebo on all measures
- Nausea, insomnia, headache commonest SE

Sunovion data on file.
RESOLVE Study
MADRS (MMRM) – Primary Endpoint

Baseline  Wk 1  Wk 2  Wk 3  Wk 4  Wk 5  Wk 6

Effect Size = 0.80

LS Mean Change from Baseline

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

Placebo (N=100)  Lurasidone (N=108)

BL mean = 33.3  BL mean = 33.2

ITT Population

Sunovion data on file.
Bipolar I Depression: MADRS Total Score Over 8 Weeks for Aripiprazole or Placebo

Mean Change in MADRS Total Score Over 8 Weeks

<table>
<thead>
<tr>
<th>Weeks</th>
<th>Baseline</th>
<th>Study</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>28.49</td>
<td>29.07</td>
<td>Study 1</td>
</tr>
<tr>
<td>Study 1</td>
<td>29.35</td>
<td>29.56</td>
<td>Study 2</td>
</tr>
</tbody>
</table>

P=NS at Week 8; * P ≤ .05; ** P < .01; vs BPO.
AR1=aripiprazole. ARI unapproved for acute bipolar depression.
Ziprasidone Monotherapy Not Efficacious in Acute Bipolar Depression

*P<.05. ZIP=ziprasidone. ZIP unapproved for acute bipolar depression.
Conventional Antipsychotics Increase Severity of Depression/Dysphoria

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

<table>
<thead>
<tr>
<th>Topic</th>
<th>Jadad score&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Evidence level&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antidepressant monotherapy</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Adjunctive antidepressants: short-term efficacy in acute depression</td>
<td>4</td>
<td>B</td>
</tr>
<tr>
<td>Predictors of initial response to adjunctive antidepressants</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Adjunctive antidepressants: maintenance studies</td>
<td>3.5</td>
<td>C</td>
</tr>
<tr>
<td>Predictors of long-term responsiveness to adjunctive antidepressant treatment</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Antidepressant use in mania and mixed states</td>
<td>3</td>
<td>D</td>
</tr>
<tr>
<td>Antidepressants and affective switch (mania, hypomania, or mixed)</td>
<td>4</td>
<td>C</td>
</tr>
<tr>
<td>Are newly emerging or increasing irritability and agitation, subclinical mixed states during antidepressant treatment a form of mood switching?</td>
<td>3.5</td>
<td>D</td>
</tr>
<tr>
<td>Antidepressants and cycle acceleration</td>
<td>3.5</td>
<td>D</td>
</tr>
<tr>
<td>Antidepressants and suicidality</td>
<td>3</td>
<td>D</td>
</tr>
</tbody>
</table>

<sup>a</sup> The Jadad score indicates study methodological quality from 0 to 5, with higher scores indicating higher quality.  
<sup>b</sup> Grades for evidence level from A (excellent) to D (poor).  

Pacchiarotti et al. 2013.
Adjunctive Levothyroxine in Bipolar Depression: A Randomized, Double-Blind, Placebo-Controlled Study

Total study group (n=62)

- Placebo (n=31)
- Levothyroxine (n=31)

Women (n=32)

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

Men (n=30)

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

*HAMD=Hamilton rating scale for depression.

*p<0.05 vs placebo (ITT; LOCF).

Adjunctive levothyroxine (300 µg/day) or placebo in patients with bipolar I or II disorder.

HAM-D=Hamilton rating scale for depression.

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.
http://www.psychiatrictimes.com/bipolar-disorder/content/article/10168/1846994.
Adjunctive Armodafinil in Bipolar Depression

- 8-week randomized comparison of armodafinil 150 mg/day (n=128) vs placebo (n=129) added to lithium, olanzapine, or divalproex for bipolar depression
- Two negative studies

*P=0.027 (ANCOVA) versus placebo; **P=0.044 (ANOVA) and P=0.074 (ANCOVA) versus placebo. ANCOVA, analysis of covariance, ANOVA, analysis of variance. Calabrese JR, Ketter TA, Youakim JM, et al. J Clin Psychiatry. 2010;71(10):1363-1370.
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). Schoeyen H K, et al. *Am J Psych.* 2015;172(1): 41-51.
## 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 trials but positive meta-analyses.
**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>*Note. 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 treatment not tolerated</th>
</tr>
</thead>
<tbody>
<tr>
<td>❖ Transcranial Magnetic Stimulation (TMS)</td>
</tr>
<tr>
<td>❖ Antimanic therapy + (FDA approved medication for major depression)*</td>
</tr>
<tr>
<td>❖ Pramipexole</td>
</tr>
<tr>
<td>❖ Adjunctive – modafinil, thyroid, or stimulants</td>
</tr>
<tr>
<td>❖ 3 drug combination</td>
</tr>
<tr>
<td>*Note. There is inadequate information (including negative trials) to recommend adjunctive antidepressants, aripiprazole, ziprasidone, levetiracetam, armodafinial, or omega-3 fatty acids for bipolar depression.</td>
</tr>
</tbody>
</table>

## Numbers Needed to Treat vs Numbers Needed to Harm

<table>
<thead>
<tr>
<th></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>

# 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>
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<td></td>
<td></td>
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<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>
<td>0</td>
</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>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Neurological</strong></td>
<td></td>
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<td></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>
<td>++</td>
<td>+</td>
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<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>
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<tr>
<td><strong>Hormonal</strong></td>
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<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>

ARI=aripiprazole; ASE=asenapine; CLZ=clozapine; ILE=iloperidone; LUR=lurasidone; OLZ=olanzapine; QTP=quetiapine; RIS=risperidone; ZIP=ziprasidone.
Variables Influencing Functional Outcomes in Bipolar Disorder

- **Sociodemographic Variables**: Age, male gender, low premorbid psychosocial functioning
- **Clinical Variables**: Age of onset, # of episodes, hospitalizations, Subthreshold symptomatology, rapid cycling, medical or psychiatric comorbidity
- **Neurocognitive Variables**: Neurocognitive dysfunction (attention, verbal memory, executive functions)
- **Environmental Variables**: Social and family support, policies, perceived stigma
- **Pharmacological Variables**: # drugs, side effects

What Can Be Done to Improve Cognition and Functioning in Bipolar Disorder?

• Prevention of cognitive impairment
  – Effective pharmacotherapy for relapse prevention
  – Psychoeducation

• Treatment of cognitive impairment
  – Treating subthreshold depression
  – Treating comorbidities
  – Rational use of drugs
  – Cognitive enhancers
  – Cognitive remediation

Functional Remediation Trial in Bipolar Disorder

10 centers

Bipolar I and II patients in remission

FAST >18

A score of 4 or more in the FAST cognitive domain and 2 or more in another domain

-3 Months

Week 0

Randomization

Double-blind, randomized design

N=239

n=77

n=82

n=80

Functional Remediation

Psychoeducation

Treatment as usual

Primary endpoint: FAST change from baseline

Week 0

Week 21

Week 52

Higher scores indicate greater impairment. Functional remediation programme 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=0.065; F=6.51; P=.002) SE=standard error.
Conclusions

• Bipolar depression and mixed episodes are the predominant presentation
• Atypicals are the choice treatment in mixed features
• All atypicals are not efficacious in bipolar depression
• Psychosocial treatments are critical in most patients
• Attention to physical health outcomes is critical to preventing and treating bipolar depression: i.e. metabolic morbidity as brain hazard